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Problems Involved in the Therapeutic and Prophylactic Uses of Antibiotics—1959 — Henry Welch

The Value of the Application of Cybernetic Principles to Physiological Regulatory Mechanisms — H. Laborit and B. Weber

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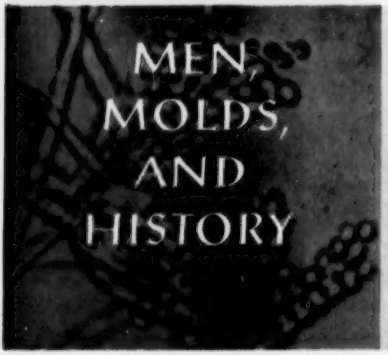

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Associate in Ophthalmology
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Problems Involved in the Therapeutic and Prophylactic Uses of Antibiotics—1959*

Henry Welch, Ph.D.

DIRECTOR, DIVISION OF ANTIBIOTICS, FOOD AND DRUG ADMINISTRATION, UNITED STATES DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
WASHINGTON, D. C.

In 1942 when penicillin was first introduced into the United States, it is questionable whether anyone realized that this event was the beginning of a new billion-dollar industry. During the first year of commercial production, about 29 pounds of penicillin were made available. In 1958, more than 800,000 pounds were produced. Total antibiotic production was more than 2.5 million pounds in 1958. Although 28 antibiotics are available for use in our country, 80 to 90 per cent of the total production is accounted for by penicillin, streptomycin, and dihydrostreptomycin and the four broad-spectrum antibiotics, chlortetracycline, oxytetracycline, tetracycline, and chloramphenicol.

It need not be emphasized here that these drugs have had very wide and, in some cases, indiscriminate use. Their remarkable curative powers, more pronounced perhaps in the early days than now, resulted in their being injected, insufflated, given by mouth, spread on every part of the body, and sprayed intra-abdominally, intrapleurally, and intravaginally; no surface or cavity of the body has remained inviolate. There are more than 450 antibiotic preparations available for clinical use today, and they run the gamut of injectables, ointments, powders, sprays, capsules, sirups, ear and eye drops, suppositories, troches, tablets, and vaginal bougies. Antibiotics have saved tens of thousands of lives in the past 14 years, and the reduction in mortality, morbidity, and complications of disease has affected the lives of millions.

The extension of the uses of antibiotics to fields other than prophylaxis and therapy of human disease has magnified the problems of the U. S. Food and Drug Administration from the standpoint of side reactions and possible significance to public health. Antibiotics are used in animal nutrition for promotion of growth in swine, chicks, and poults. Therapeutic and prophylactic use of large quantities of anti-

* To be presented at the Antibiotics Symposium, a meeting with international participation, in Prague, Czechoslovakia, May 18–23, 1959.

biotics is made for animals such as cows, beef cattle, swine, chicks, and mink. These drugs are now being used as crop sprays to prevent blight in apples, pears, walnuts, and beans and bacterial diseases of tobacco, tomatoes, peppers, and cherries. Studies have been made to show the value of antibiotics in the preservation of vegetables, fish, beef, ham, chickens, and other perishables.

The actual or potential introduction of antibiotics into the food supply poses the same problem as does the use of any other chemical, and this growing use of chemicals in food is one of the most serious problems facing the Food and Drug Administration. It should be emphasized, however, that the problem of contamination of foods with antibiotics is a small one compared with our other problems of food safety. There is virtually no limit to the expanding list of chemicals that may find their way into our food supply. Chemicals are promoted as stabilizers, preservatives, disinfectants, antioxidants, extenders, tenderizers, emulsifiers, growth promoters, fumigants, herbicides, defoliants, fungicides, miticides, bleaches, sweeteners, conditioners, colorers, and flavorers. In addition, food packages that incorporate new plastics, enamels, films, plasticizers, catalysts, and coatings are further potential sources of food adulteration.

SIDE REACTIONS

Nevertheless, with such major advances in therapy, we unfortunately have to face the accompanying untoward side reactions. These invariably follow. In the case of penicillin, a relatively atoxic drug, the "side reaction" is its potentiality for sensitizing certain unfortunate persons. Although the other antibiotics are, in general, poor sensitizers, other side reactions may occur after their administration.

It is estimated that about 10 per cent of our population has a tendency to become sensitive, in the course of a lifetime, to some food, drug, cosmetic, or other substance, while the great majority of persons do not. Within this 10 per cent there is a great variation in susceptibility to sensitization. Some acquire it easily, while others are more resistant. Some may be sensitive on first contact (the atopic group), while others require one contact, and still others may require several contacts, before exhibiting a reaction. The reactions, too, vary in degree from mild, transient rashes to prolonged urticaria and from a brief asthmatic attack to fatal anaphylactoid shock. Allergic manifestations occur less frequently in children.

Antibiotics are probably our most important and most widely used therapeutic agents. It is unlikely that any one of us will go through life without having antibiotics administered to him for sound medical reasons. Thus, with a population for the United States of more than 170 million, we are concerned primarily with perhaps 17 million people who may react to a contact with antibiotics, be it through therapeutic use or, inadvertently, through eating or drinking foods containing them. In the first case the physician and patient have a choice, but in the latter instance there is none.

ANTIBIOTICS IN ANIMAL FEED

Antibiotics used for stimulation of growth are usually present in feed in small

amounts (5 to 20 parts/million). When antibiotics are used in these quantities, antibiotic residues are not found in the blood or tissue of the animals. When 50 to 200 parts/million are used for prophylactic or therapeutic purposes in feed for chicks or poults, residues may be demonstrated in the tissues during the period in which the animal is being fed these higher concentrations. However, the antibiotics are rapidly excreted within a few days after the drug is withdrawn. The use of antibiotics as just described, under present normal marketing conditions, does not, in our opinion, constitute a public health hazard. Antibiotics used as crop sprays are dissipated before the edible portion of the plant is formed, and since they do not reach the consumer, no public health problem is involved.

FOOD PRESERVATION

Extensive experiments have been conducted to explore the potentialities of antibiotics as food preservatives. In November, 1955, the Food and Drug Administration approved the use of chlortetracycline for the preservation of raw poultry, and about one year later, similar approval was given for oxytetracycline. Tolerance levels for these drugs were established under the provisions of the Miller Pesticide Chemicals Amendment to the Food, Drug, and Cosmetic Act, passed by the Eighty-third Congress in 1954. These drugs act as preservatives and extend the "shelf life" of the fowl.

Under the Miller Amendment, the applicant must demonstrate "usefulness" to the satisfaction of the Department of Agriculture and "safety" to the Food and Drug Administration. The tolerance level for both chlortetracycline and oxytetracycline in the raw bird was established at 7 parts/million, in any part of the bird. Before approval of this tolerance level was granted, it had to be shown that no significant antibiotic residues could be found in the poultry after cooking by broiling, frying, boiling, or baking. A considerable number of investigations of the usefulness of antibiotics in the preservation of fish and meats have also been completed. However, approval of such uses by the establishment of tolerance levels under the Miller Amendment can be obtained only when conclusive evidence is presented that such use is not detrimental to the health of the general public.

INDIRECT ADULTERATION

In addition to being directly introduced in these ways into the food supply, antibiotics may also find their way into foods indirectly. In 1948 it was first noted that when milk from cows that had been treated for mastitis by intramammary infusion was mixed with antibiotic-free milk for the purpose of making cheese, failure to produce a satisfactory cheese product often resulted. This was due to the inhibition of the starter culture used in cheese manufacture by the antibiotic present in the milk. Realizing that antibiotics might also reach the consumer by way of milk, the Food and Drug Administration, by regulation, required that mastitis preparations carry a warning in their labeling to the effect that "milk from treated segments of udders should be discarded or used for purposes other than human consumption for at least 72 hours after the last treatment."

Very large amounts of antibiotics are used in the treatment of milk-producing cows infected with mastitis. It is estimated that more than 75 tons of these drugs are used yearly in the United States in the treatment of this widespread infection. The great bulk of infected cows are treated by udder infusion, and a variety of products are available for this purpose. Penicillin is perhaps used in the greatest volume, since this drug is quite effective in those cases caused by streptococci, particularly *Streptococcus agalactiae*, the organism responsible for most cases of mastitis. However, the disease is also caused by other organisms, such as the corynebacteria and the *coli-aerogenes* group of organisms, and, as a result, other antibiotics, such as dihydrostreptomycin, streptomycin, the tetracyclines, neomycin, polymyxin, and bacitracin, and the sulfonamides are used for treatment and prophylaxis.

Treatment usually consists of application of a single tube or injection of a syringe full of the preparation for each infected quarter of the udder, but as many as four treatments, at 12-hour intervals, may be necessary per quarter. Thus, in a single treatment, an animal that is being treated with a combination preparation could be given 500,000 units of penicillin, 500 mg. of dihydrostreptomycin, 50 mg. of neomycin, and 750 mg. each of sulfanilamide and sulfathiazole. If the infection is severe, the animal may receive as much as four times these amounts within a 48-hour period.

When the antibiotic preparation used is effective, the clinical result is quite dramatic, and a marked change in the appearance of the teat and udder takes place within 24 hours. However, the disappearance of the signs of infection and the consequent reduction of inflammation are no guarantee that the infection is eliminated. This can be determined only by bacteriological examination of the milk. Certainly, a favorable change in appearance of the infected udder is no guarantee that the drugs infused have been completely absorbed or eliminated. As a matter of fact, experimental evidence points to the opposite conclusion. It is necessary to milk infected cows twice daily for a period of at least three days to be sure that the great bulk of the drugs has been milked out. Experience has shown that practically the entire amount of infused antibiotic is eliminated by regular milking over a period of three days. It appears that failure to observe the warning given in the labeling of mastitis preparations concerning the discarding of milk from treated cows is largely responsible for the presence of antibiotic residues in the milk supply.

SURVEYS AND SOLUTIONS

In 1954, 1955, and 1956, national surveys were made of fluid market milk to determine its antibiotic content. In these surveys a total of 2274 samples were examined, and samples from all states were included. An average of 6.9 per cent of the samples examined contained penicillin, in concentrations varying from 0.003 to 0.550 units/ml. Other dairy products tested, including powdered milk, evaporated milk, ice cream, butter, cheese, shell eggs, and broken eggs, were found to be free from antibiotic residues.

The relatively large number of positive samples noted in the year that separated the first and second surveys caused some concern, and it seemed advisable to obtain some opinion on the possible public health significance of the presence of penicillin

in these quantities in market milk. Accordingly, some 30 experts in the fields of antibiotic therapy, allergy, and pediatrics were asked to express their views on this matter. The majority of these experts expressed the opinion that penicillin in these amounts is unlikely to modify the oral or intestinal flora, cause the emergence of resistant strains, or provoke sensitization of an insensitive person. However, the majority felt that such concentrations might possibly cause a reaction in a highly sensitive person. In 1957 the Food and Drug Administration took three steps to alleviate the public health problem involved:

1. Through cooperation with the U. S. Department of Agriculture, an intensive program was initiated to educate the farmer concerning the importance of discarding, or using for purposes other than human consumption, milk from cows treated for mastitis with antibiotic drugs for a period of three days after the last treatment. In addition, the National Milk Producers Federation, which reaches some 500,000 farmers, assisted in this educational program through their state agents.

2. On Jan. 23, 1957, a regulation was adopted requiring that the warning statement regarding disposition of milk from treated cows be placed on the immediate container of the drug rather than in the literature accompanying it.

3. On Aug. 12, 1957, the penicillin content of mastitis preparations was limited to 100,000 units/dose.

About one year has elapsed since these three steps were taken, and a survey just completed shows that there has been a marked reduction in the number of samples found to contain penicillin and other antibiotics (from 6.9 per cent to about 3 per cent). Although this does indicate an improvement in the situation, only complete elimination is considered to be satisfactory from a public health standpoint if protection from possible reactions is to be afforded the hypersensitive person.

As early as 1945 isolated reports of acute anaphylactoid reactions after administration of penicillin began to appear in the literature and a relatively high percentage of these terminated fatally. With the passage of time and with several hundred tons of this highly antigenic drug being prescribed annually, more and more severe reactions are being encountered.

In a spot survey in the United States made in 1952 and 1953 in 11 cities of 100,000 population or more, we found 88 cases of anaphylactoid shock, of which 25 (28 per cent) were fatal. None of these had been reported in the literature. The survey covered 95 hospitals with a total capacity of 51,000 beds. Penicillin was found responsible for 84 of the reactions, while four followed the administration of streptomycin. None of the broad-spectrum antibiotics was involved in any of the cases. It was obvious from this spot survey that injectable preparations were by far more likely to cause anaphylactoid shock, since we encountered only one such reaction due to oral penicillin. Furthermore, patients with a history of bronchial asthma, hay fever, or other allergies or a previous reaction to penicillin appeared to be most likely to exhibit this serious type of reaction.

In 1957 a more extensive nationwide survey than the previous one was completed. It was designed to include a total of more than 800 hospitals and interviews with more than 1600 physicians. In contrast to the earlier survey, in which only anaphylactoid reactions caused by antibiotics were investigated, the present one was

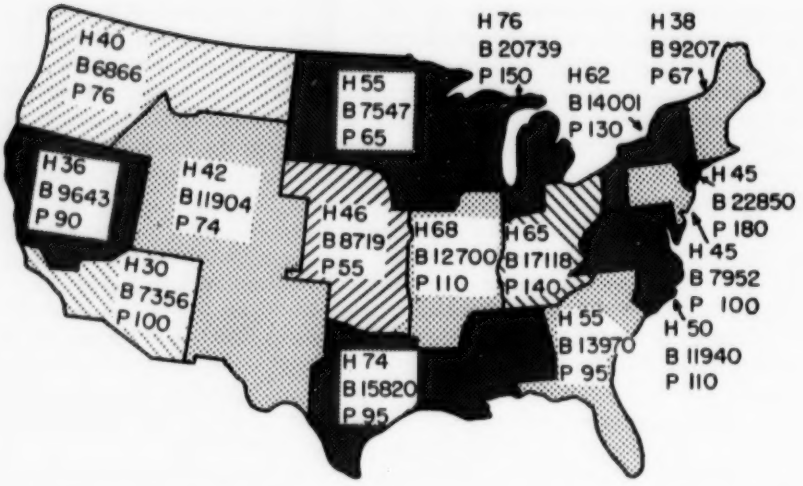

FIG. 1. Geographical distribution of physicians and hospitals visited. H = hospitals (total 827); B = beds (total 198,332); P = physicians (total 1637).

directed at all severe reactions, including blood dyscrasias, exfoliative dermatitis, severe angioneurotic edema, severe monilial or fungal infections, and enterocolitis associated with antibiotic medication.

Each of the 16 district areas of the Food and Drug Administration, which geographically cover the entire country, was assigned a proportionate number of physicians and hospitals to visit, and all case reports and other pertinent data were obtained by trained investigators, each familiar with the most likely sources of such information in a particular locality. Because of this, the number of cases "missed" in the areas investigated was probably small. None of the reactions reported in this survey has been recorded in the literature. The geographical distribution of physicians and hospitals visited is shown graphically in the map of the country in figure 1. It should be noted that approximately one third of the hospital beds available in general hospitals in the United States were included in this survey. On this map, state lines have been obliterated and the borderlines of the Food and Drug Administration district areas are shown. Each district office spread its physician and hospital contacts throughout their areas to obtain the most representative distribution.

When an inspector encountered any type of serious reaction to antibiotics, he obtained the patient's medical history, including age, sex, past illnesses, drugs, and amounts used for the disease being treated, and the amount and kind of antibiotic administered when the reaction occurred. If the patient was hospitalized, pertinent information from all hospital records was recorded. This included case summary sheets, the physician's order sheet, all laboratory reports, nurses' notes, if pertinent,

TABLE I

Cases Classified as Not Severe

	Angio-neurotic edema and urticaria	Other dermal lesions	Serum sickness-type reaction	Diarrhea	Local monilíasis	Total
Penicillin	1224	319	65	2	6	1616
Combined antibiotics*	85	34	5	15	21	160
Tetracycline	17	4	1	27	7	56
Oxytetracycline	9	3	0	22	4	38
Chlortetracycline	5	0	0	7	6	18
Novobiocin	6	6	0	2	0	14
Erythromycin	5	1	0	3	0	9
Streptomycin	4	5	0	0	0	9
Chloramphenicol	3	0	0	0	1	4
Neomycin	0	0	0	1	0	1
Total	1358	372	71	79	45	1925

* Mostly combinations of penicillin and streptomycin or dihydrostreptomycin.

and, if the patient died, a copy of the autopsy report, if available. In addition, the complete facts surrounding prior treatment were determined by interviews with the attending physician and, if necessary, by interviews with the patient or the family.

During the survey, which covered all severe reactions occurring from late 1953 to early 1957, 3419 case histories were collected and classified. Of these, it was necessary to discard 424 because of insufficient data for classification, or because

TABLE II

Antibiotic Reactions Encountered and Classified During Survey

	No. cases	Total cases
Life-threatening cases		
Anaphylactoid reactions	809	
Superinfections	107	
Skin reactions	70	
Blood dyscrasias	46	
Angioneurotic edema with cerebral or respiratory involvement	38	
		1070
Non-life-threatening cases* (largely angioneurotic edema)		1925
		2995†

* See table I for classification.

† In addition, 424 cases were discarded for lack of data or because antibiotics were not involved or because they did not fall in the period covered by the survey.

TABLE III

Preparations Associated with Anaphylactoid Shock

	Cases	Deaths	Year anaphylactoid reactions occurred					
			1953	1954	1955	1956	1957	Unknown
Penicillin preparations			24	179	231	301	60	14
Intramuscular injection*	611	63						
Intramuscular with streptomycin or dihydrostreptomycin†	122	9						
Intravenous injection with streptomycin	1	0						
Tablets	35	0						
Troches	4	0						
Capsules	7	0						
Oral suspension	3	0						
Inhalation	4	0						
Ointment	1	0						
Nose drops	1	0						
Skin test	1	0						
Dental paste (with bacitracin, dihydrostreptomycin, and streptomycin)	2	0						
Syringe contaminated with penicillin	1	0						
Total penicillin preparations	793	72						
Other preparations								
Streptomycin, intramuscular	9	1						
Dihydrostreptomycin, intramuscular	3	1						
Chloramphenicol capsules	1	0						
Tetracycline capsules	1	0						
Tetracycline in oil (oral)	1	0						
Tetracycline, intramuscular, or testosterone, intramuscular	1	0						
Total other preparations	16	2						
Total all preparations	809	74 (9.1% deaths)						

* Tetanus antitoxin also involved in 6 of these cases.

† Tetanus antitoxin also involved in 3 of these cases.

antibiotics were not involved, or because the reaction occurred outside the survey period. Because of the strict criteria established for the "severe" reactions, it was necessary to exclude another 1925 cases (table I). It should be noted, however, that many of these cases were considered by the attending physicians as severe reactions and, of course, had we considered the patient's judgment, all would have been classified as severe. The exclusion of this group of 1925 cases was necessary, however, because in classifying the reports only those reactions that were actually life-threatening were graded as severe. This does not imply that we consider the others minor reactions from the standpoint of the hazard that would be involved from future exposure to the same antibiotic. This applies particularly to penicillin.

Of the 1070 reactions classified as severe, more than 800 were of the anaphylactoid type. Superinfections, severe skin reactions, blood dyscrasias, and angioneurotic edema with respiratory involvement comprised the remainder. These are tabulated in table II. The antibiotic preparations associated with anaphylactoid shock are shown in table III.

Of 809 anaphylactoid reactions, 793 were the result of the administration of penicillin preparations. As noted in table III, there is a definite increase in the number of reactions from 1953 through 1956, the greatest number, 301, occurring in the latter year. Twelve cases were the result of intramuscular injections of streptomycin or dihydrostreptomycin. One was associated with capsules of chloramphenicol and 1 with capsules of tetracycline. One reaction followed an intramuscular injection of tetracycline administered along with testosterone in oil.

Because of the rarity with which the broad-spectrum antibiotics have been implicated in allergic reactions, the pertinent data collected on 1 case associated with chloramphenicol and 3 cases associated with tetracycline are given.

CASE REPORTS

Case 1. One hour prior to admission to a hospital, a 39-year-old white man had taken one 250 mg. capsule of tetracycline prescribed by his physician for an upper respiratory infection. Twenty minutes after ingesting the capsule, he developed generalized hives and difficulty in breathing. Blood pressure dropped 85/60 mm. of mercury. Initial examination showed an acutely ill man in state of shock. The skin was covered with hives. He was placed on intravenous hydrocortisone, ACTH, and levarterenol. In 12 hours the hives had disappeared and within 24 hours blood pressure was stable without levarterenol. He was kept under observation for three days, during which time he received decreasing amounts of cortisone and ACTH. He was discharged with the warning never to take any antibiotic again.

Case 2. An 18-year-old boy developed a fever and acute upper respiratory infection. His physician gave him a bottle of tetracycline suspended in coconut oil (250 mg./teaspoonful, physician's sample). The patient took 1 teaspoon while the physician was present, after which he became nauseated and vomited some of the medication. He then developed generalized itching, shortness of breath, and lowered blood pressure. A second physician was called and together they treated the patient with injections of adrenaline, ACTH, and chlorprophenpyridamine maleate. The patient responded and hospitalization was not necessary.

Case 3. A 30-year-old white woman was admitted to hospital because of collapse after receiving two injections, one of tetracycline and one of testosterone. A few minutes after the injections she began to feel "funny" all over and her limbs and hands became numb. She broke out in a cold sweat and started to vomit and then became unconscious. She was brought to the hospital by ambulance. The patient had a history of undulant fever for a period of eight years during which time she had been treated with tetracycline. On admission she had a blood pressure of 80/60 mm. of mercury. Pulse was unobtainable at the wrist but was heard at the apex and was 96. She was treated with adrenaline, cortisone, levarterenol, and oxygen. She recovered and was discharged within 48 hours. This case was classified as a reaction to tetracycline, since it appeared to be the most likely drug in view of the previous history of administration of tetracycline for the treatment of undulant fever. No sensitivity tests to either tetracycline or testosterone were carried out.

Case 4. A 51-year old white woman (a hospital nurse) was admitted unconscious to the medical service. The patient had developed a mild sore throat and decided she was getting a cold. In the past the patient had taken chloramphenicol for colds with good results, so she decided to try it again. She took two 250 mg. capsules every six hours for three doses while at work. The next morning the patient came to work at 7:00 A.M. and, still feeling effects of the cold, took two 250 mg. capsules of chloramphenicol and no other medication. At about 8:30 A.M. the patient was walking down the hall on the third floor of the hospital when she had a sudden attack of vertigo, which ended in syncope with the patient falling on the floor.

TABLE IV

Anaphylactoid Reactions by Age Group and Sex*

Age group, yr.	Male	Female
Penicillin preparations		
1–12	30	16
13–25	55	56
26–35	68	82
36–45	65	90
46–55	81	50
Older than 55	88	61
Age unknown	22	29
	409	384
Other antibiotic preparations		
1–12	0	0
13–25	1	0
26–35	1	2
36–45	1	3
46–55	2	2
Older than 55	2	1
Age unknown	0	1
	7	9

* Youngest person, 2 weeks; oldest person, 89 years.

The pulse was weak and thready; blood pressure, 85 to 90 mm. of mercury systolic; and skin, cold and moist. All evident signs of shock were present. Artificial respiration was started, an airway maintained, and adrenaline injected. The patient was put to bed, oxygen was given, and she was closely watched. The pressure rapidly rose and shock subsided. By 11:30 A.M. the patient had responded and then lapsed into sleep. She recovered after further treatment with cortisone.

There were 611 anaphylactoid reactions after intramuscular injection with 63 deaths. One reaction followed an intravenous injection of procaine penicillin and streptomycin. This highly questionable procedure of injecting an insoluble salt of penicillin intravenously was fortunately not fatal. There were 122 anaphylactoid shocks that followed intramuscular injection of penicillin in combination with streptomycin or dihydrostreptomycin. Nine of these were fatal. Thus, there were 733 reactions after intramuscular injection of penicillin or penicillin in combination with streptomycin or dihydrostreptomycin, and, of these, 72 patients died (approximately 10 per cent).

There were 49 reactions of the anaphylactoid type after oral administration of penicillin preparations, and none of these was fatal. Four reactions followed administration of penicillin by inhalation, one occurred after application of penicillin ointment, one followed the use of nose drops, and one followed a skin sensitivity test. Two were the result of the application of a dental paste used in root canal therapy containing penicillin, bacitracin, streptomycin, and dihydrostreptomycin.

One patient went into anaphylactoid shock after the use of a syringe contaminated with penicillin, emphasizing that extremely small amounts of this antibiotic can "trigger" this reaction. One case involved a woman who prepared a penicillin tablet in a sugar solution for her granddaughter. She tasted the solution to determine whether it was sweet enough and quickly went into shock. Another person who had had an anaphylactic shock a year previously had a second one when he tasted an oral suspension of penicillin refused by a child. Another 39-year-old white woman had an acute anaphylactoid shock within 10 minutes after starting to suck a penicillin troche. This woman had had a similar reaction a few months previously from an intramuscular injection of penicillin. One person went into typical anaphylactoid shock a few minutes after application of penicillin ointment to a skin abrasion.

Anaphylactoid reactions occurred with about equal frequency in men and women. Of the 793 reactions associated with penicillin preparations, 409 occurred in men, 384 in women. Of the anaphylactoid reactions after administration of other antibiotic preparations, 7 occurred in men and 9 in women. As shown in table IV anaphylactoid reactions involved all age groups, although the fewest occurred in children 12 years of age and younger.

The second largest group of "life-threatening" reactions associated with antibiotic therapy was the group of superinfections. A total of 107 cases were classified in this

TABLE V

Severe Superinfections

	Drugs involved*								
	Tetracyclines and other drugs†	Tetracyclines	Combined antibiotics except tetracyclines‡	Penicillin	Erythromycin	Neomycin	Total	After abdominal operation	Deaths
Staphylococcal enterocolitis	52	11	9	1	1	0	74	44	26
Enterocolitis (no cultures)	11	11	2	0	0	1	25	15	13
Moniliasis, intestinal	3	0	0	1	0	0	4	0	0
Dermal	0	1	0	1	0	0	2	0	0
Pulmonary	1	0	1	0	0	0	2	0	1
							107	59	40

* The great majority of the preparations used here (90 per cent plus) were given orally. In most instances in which penicillin or a combination of penicillin and streptomycin was involved the drug was administered parenterally.

† Other drugs consisted of one or more of the following: penicillin, streptomycin, dihydrostreptomycin, neomycin, chloramphenicol, erythromycin, bacitracin, novobiocin, and sulfonamides.

‡ Consisted of combinations of two or more of the following: neomycin, bacitracin, penicillin, streptomycin, chloramphenicol, and sulfonamides.

TABLE VI

Severe Skin Reactions

	Exfoliative dermatitis		Anaphylactoid or hemorrhagic purpura		Erythema multiforme*		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Penicillin	33	4	11	0	3	1	47	5
Penicillin with other drugs	13	1	4	0			17	1
Streptomycin	3	0					3	0
Novobiocin	1	0					1	0
Chloramphenicol with other drugs			1	0			1	0
Tetracycline with other drugs	1	1					1	1
Total cases	51	6	16	0	3	1	70	7

* Two of bullous type, 1 fatal.

group. There were 74 cases of staphylococcal enterocolitis and 44 of these followed an abdominal operation. In this series of cases there were 26 deaths and 18 of these patients had had abdominal surgery. As shown in table V, another 25 cases were classified as enterocolitis, and although staphylococci may have been involved, cultures of the stools were not made. There were 13 deaths in this series, 9 of which followed abdominal operations.

Thus, of 107 superinfections, 99 were cases of enterocolitis, 59 of which followed abdominal operations, and 39 had a fatal outcome.

There were 4 cases of severe intestinal moniliasis, 2 cases of pulmonary moniliasis (1 death), and 2 cases of severe and extensive dermal moniliasis. In both of the latter cases moniliasis started as a localized lesion (perianal) and subsequently spread to practically the entire body, persisting in 1 case for several months.

In table VI are recorded the 70 severe skin reactions that were encountered in the survey.

In this group there were 7 deaths (10 per cent), 6 after exfoliative dermatitis and 1 after erythema multiforme of the bullous type. Penicillin alone was associated with 33 cases of exfoliative dermatitis and with other drugs in 13 more for a total of 46. Tetracycline with other drugs was associated with 1 case of exfoliative dermatitis, which was fatal.

There were 16 cases of anaphylactoid or hemorrhagic purpura with no deaths. Eleven of these cases were associated with penicillin alone and 4 others involved penicillin and other drugs. One was associated with chloramphenicol. There were 3 cases of erythema multiforme of which 2 were of the bullous type, 1 ending fatally.

In the survey, which covered a period of nearly four years, a total of 46 severe blood dyscrasias was reported and classified. Of these, 27 patients died, a death rate of more than 50 per cent. These cases are recorded in table VII.

Chloramphenicol was associated with 12 cases of aplastic anemia, 9 of which were

fatal, 3 cases of granulocytopenia with 1 death, and 1 fatal case of thrombocytopenic purpura. There were 19 cases of aplastic anemia (14 deaths) with which chloramphenicol was associated, but a variety of other drugs was also involved and therefore it was impossible to implicate any one drug with certainty. There were 3 patients in this group who quite possibly developed the blood dyscrasia through contact with other chemical agents. One of these patients had a history of heavy exposure to insecticides (he was a taxidermist), the second had used a hair dye every six weeks for 10 years, while the third had a history of exposure to radium, arsenicals, and insecticides. Chloramphenicol with other drugs was associated with 3 cases of granulocytopenia, 2 cases of thrombocytopenic purpura, and 1 of leukopenia; none of these was fatal.

There were 2 cases of granulocytopenia, 1 associated with the use of three antibiotics—penicillin, streptomycin, and oxytetracycline—and the other with tetracycline alone. The latter was fatal. There were 3 cases of thrombocytopenic purpura, 1 associated with penicillin alone, 1 with penicillin, streptomycin, and sulfonamide drugs, and the third with novobiocin, penicillin, and sulfonamide drugs.

Of the 16 blood dyscrasias associated with chloramphenicol alone, 1 occurred in 1953, 6 in 1954, 3 in 1955, and 6 in 1956. Nine of these occurred in children younger than 12 years of age, 7 of whom were white girls. Of the 2 boys, one was a Negro

TABLE VII

Blood Dyscrasias

	Aplastic anemia		Granulocytopenia		Thrombocytopenic purpura		Leukopenia		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Chloramphenicol	12	9	3	1	1	1			16	11
Chloramphenicol with other drugs*	19	14	3	0	2	0	1	0	25	14
Penicillin					1	0			1	0
Penicillin-streptomycin-oxytetracycline			1	0					1	0
Penicillin-streptomycin and sulfonamide					1	0			1	0
Novobiocin-penicillin and sulfonamide					1	1			1	1
Tetracycline			1	1					1	1
Total cases	31	23	8	2	6	2	1	0	46	27

One patient in the "chloramphenicol with other drugs" category had a source of supply for most all drugs. He was believed to have taken quite a number of chloramphenicol capsules without a prescription. Included in the "chloramphenicol" group is a patient who had a prescription refilled five times without authorization of a physician.

* One patient in this category had no other drugs but had a history of heavy insecticide exposure. Another had no other drugs but had used a hair dye every six weeks for 10 years, while a third had a history of exposure to radium, arsenicals, and insecticides.

TABLE VIII

Angioneurotic Edema with Respiratory or Cerebral Involvement

	Cases	Deaths
Penicillin preparations		
Intramuscular	26	3
With streptomycin or dihydrostreptomycin intramuscularly	5	
Oral	6	1
Total penicillin preparations	37	4
Other preparations		
Chloramphenicol intramuscularly	1	1
	38*	5

* Equal numbers of men and women involved. No significance in age group distribution.

and the other white. This is in agreement with our previous survey in which white girls in this age group were found to be most frequently involved. Although both men and women of a variety of ages developed blood dyscrasias after antibiotic therapy, we were impressed with the frequency with which this complication occurred in the frail type of girl younger than 12 years of age with a history of many illnesses and/or a history of asthma or other allergies.

There were 38 life-threatening cases of angioneurotic edema, 37 with severe respiratory and 1 with cerebral involvement. Thirty-seven of these followed administration of penicillin and 1 followed intramuscular chloramphenicol. There were 5 deaths in the group, a fatality rate of about 13 per cent. The only death encountered after oral penicillin therapy occurred in this group. It should be recalled that in this survey there were more than 1300 other cases of angioneurotic edema largely due to penicillin (table I). None of these had respiratory or cerebral involvement and thus were not classified as life-threatening in accordance with the strict criteria to which we adhered. Analysis of the 38 cases recorded in table VIII indicated no significant differences in sex or age group distribution.

DISCUSSION

Those who have made a study of the production, use, and side reactions due to the administration of antibiotics have been convinced that the number and severity of such reactions have been on the increase for several years. In 1956 about 1,967,000 pounds of antibiotics were produced in the United States, and although there are 17 different antibiotics clinically available, penicillin accounted for 631,000 pounds (32 per cent) of the total produced. Production of penicillin during the years encompassed by the nationwide survey reported here was as follows: 1953, 753,000 pounds; 1954, 631,000 pounds; 1955, 455,000 pounds; and 1956, 631,000 pounds.*

* As reported by the U. S. Tariff Commission.

Until 1945 we had only one type of penicillin preparation (the injectable sodium or calcium salt). Today we have more than 120 preparations commercially available. In the present survey it is believed that a representative and fair sampling of the country has been made. Each state and the District of Columbia have been included, and of the total 685,655 general hospital beds available in this country, approximately 29 per cent, 198,332, have been covered. A total of 3419 case histories of reactions were reported as severe by the physician or hospital involved. Of these, 424 cases were eliminated mainly for lack of data for proper classification. Of the remaining 2995 cases, 2517 were associated with the use of penicillin. Thus, penicillin was involved in 80 per cent of all reactions reviewed in this survey.

There were 1925 reactions that were not classified as life-threatening, and in 1616 of these, penicillin was the responsible agent. These agents were mainly cases of angioneurotic edema and other dermal lesions.

One thousand and seventy cases were classified in the survey as severe or life-threatening, and of these, penicillin was involved in 901 (84 per cent). Of the 901 penicillin cases, 83 patients died, a fatality rate of about 9 per cent. The great majority of severe penicillin reactions were of the anaphylactoid shock type (793), with a fatality rate of 9 per cent. No deaths occurred in the cases involving oral penicillin. Sixteen anaphylactoid reactions with 2 deaths were associated with other antibiotics. The incidence of anaphylactoid reactions increased during the three years fully covered in this survey: 179 cases in 1954, 231 in 1955, and 301 in 1956.

From this brief discussion, it is obvious that penicillin is the antibiotic causing the greatest number of reactions and the one most frequently involved in fatal cases. It is clear also that the oral route is the much safer method of administration, from the standpoint of both numbers of reactions and mortality. Anaphylactoid reactions from penicillin have increased in frequency during the past few years, which emphasizes the importance of having a clear-cut indication before use of this drug. Much has been said concerning wide and indiscriminate use, but there is not only the guilt of indiscriminate usage but also guilt of substance, for it is apparent that penicillin is a highly antigenic drug.

The three anaphylactoid shocks after tetracycline therapy and one after administration of chloramphenicol were a source of considerable interest and careful study. Allergic reactions of any type are extremely rare after administration of these drugs, and to our knowledge, anaphylactoid reactions have not been reported previously. It was for this reason that pertinent data in the histories of these 4 cases were included in this report. In each instance the patient involved exhibited classical symptoms of anaphylactoid shock. The history of administration of the drug involved and onset of reaction are clear. Except for the 1 patient who received testosterone in addition to tetracycline, no other drugs appeared to be involved in any of these cases. The patient who had testosterone had a history of undulant fever and prolonged treatment with tetracycline prior to the reaction. In all 4 cases it was the opinion of the physician in charge that the reaction was anaphylactoid and the result of administration of the drug specified.

There seems to be no doubt that allergic reactions to the broad-spectrum drugs do occur even though rarely, and if only on theoretical grounds, it must be accepted

that the ultimate in allergic response or anaphylactoid reaction can follow administration of these drugs in the highly sensitive subject.

Of the 107 superinfections classified in the survey as life-threatening, 99 were cases of enterocolitis in 74 of which staphylococci were isolated, again emphasizing the problem of the resistant hospital staphylococci. Eighty-five cases in this group were associated with oral administration of one or more of the tetracyclines. In the majority of cases (59), the enterocolitis followed abdominal surgery. The fatality rate was quite high in the enterocolitis group (about 40 per cent), which is in accordance with previous experiences with this serious type of reaction. Eight cases of severe moniliasis were reported, 4 intestinal, 2 dermal, and 2 pulmonary. One of the latter cases was fatal. Based on our data, however, it is quite evident that secondary infections due to fungi (particularly the monilia) are infrequent and do not constitute a serious problem with antibiotic therapy.

Of the 70 severe skin reactions, exfoliative dermatitis was most frequently encountered (51 cases). In addition, 16 cases of anaphylactoid purpura and 3 cases of erythema multiforme were reported. The over-all fatality rate for the group was 10 per cent.

During the past few years, there has been an increase in the use of chloramphenicol in the United States. That this use has been under careful supervision and selection appears to be substantiated by the few blood dyscrasias (16 cases) associated with chloramphenicol alone over the period under survey. It is not possible to implicate specifically the causative agent in the 25 cases recorded as having been associated with chloramphenicol and other drugs and chemicals. In some cases, the prolonged exposure of the patient to hair dyes, arsenicals, or radiation is strongly suggestive. The data obtained regarding the age and sex of patients developing a blood dyscrasia substantiate our previous findings, namely, that white children younger than 12 years are most frequently affected. Furthermore, girls are two or three times more frequently involved than boys, and usually there is a history of prolonged or frequent illnesses including various allergic disorders.

Of the 1396 cases of angioneurotic edema reported in this survey, only 38 had respiratory or cerebral involvement. These were classified as life-threatening. Thirty-seven of these followed the administration of penicillin and 1 followed chloramphenicol. In this group occurred the only fatality from oral penicillin.

In looking at this survey broadly, it is apparent that penicillin is the main offender from the standpoint of incidence and severity of side reactions. The survey covered hospitals comprising roughly one third of all the general hospital beds available in the United States, and a total of 2517 penicillin reactions were classified of which 901 were considered life-threatening. Although there were isolated instances of misuse, wives taking drugs prescribed for husbands and vice versa and neighbors giving intramuscular injections to each other, these cases were in the minority. The great majority of reactions occurred after administration of the antibiotic under the supervision of a physician. In spite of the number of reactions, and they loom large when viewed alone, it must be realized that the survey covered a three-year period during which approximately 600 tons of penicillin were produced for human use, equivalent to more than two billion average daily dosages of 300,000 units.

In the United States there has been in the past two years more discriminating and careful use of penicillin. In 1958 we certified as bulk drug more than 4000 Kg. less than we did in 1957. Furthermore, there has been a wider use of oral penicillin preparations, which are less likely to provoke sensitization. It appears that in the past two years there has occurred a "leveling off" and stabilization of the use of antibiotic drugs generally, and further wide swings in production and usage are not anticipated in the United States. Barring the discovery and development of a new and spectacular antibiotic, we are probably due for a period of retrenchment, during which time there will be ample opportunity to consolidate our therapeutic advancements and to mend our broken therapeutic fences.

The extension of the uses of antibiotics into areas other than the treatment and prevention of disease has not created any serious problem from a public health standpoint in the United States. The use of antibiotics for nutritional purposes in animal feeds, in agriculture, and in the preservation of poultry has not caused difficulty during the few years such uses have been in effect. However, it is apparent that the highly antigenic drug, penicillin, which has reached our milk supply through its use in dairy cattle, has provoked a definite public health problem for those unfortunate persons sensitive to this antibiotic. During the past four years, largely through education of the farmer, the incidence of milk samples containing penicillin has been lowered. Our objective, of course, is its complete elimination from the market milk supply, a goal that may only be reached through prohibition of the use of penicillin in mastitis preparations.

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EUTONOLOGY LABORATORY, HÔPITAL BOUCICAUT
PARIS, FRANCE

The application to physiological phenomena of the concepts and investigational means offered by cybernetics should greatly increase the understanding of these phenomena. We would like to demonstrate first that the use of a clear method of representation will furnish the biologist with a useful working tool. It will force him to set down in a precise manner the problems he intends to solve and will enable him to integrate and visualize many autoregulated functionings, the complexity of which often leads to confusion. The cybernetic representation will be thus called on to become in physiology what algebra is in mathematics.

GENERAL NOTIONS AND CONVENTIONAL REPRESENTATIONS

An "effector" is shown represented by a circle (fig. 1); its "effect" (or one selected from all the effects produced by this effector) is represented by an arrow originating from the circle (E); its "factors" are represented by arrows leading to it (A, B).

Such a system may contain a mechanism that is sensitive to the variations of the effect and that is capable of acting on one or more factors in accordance with these variations. In such a case, the factor(s) become a function of the effect, which will also remain a function of the factors that control it.

Therefore, an autoregulation exists since the variations of the effect caused by the variations of the factors will, in turn, influence the latter. The existence of such a "feed-back" mechanism acting on one of these factors is represented in figure 1 by a curved arrow originating from the effect arrow and leading to the arrow of the factor(s).

Such a mechanism permits the effect to liberate itself partly from the influence of the factor variations that determine it. Thus the feedback modifies to a certain extent the variations of these factors.

The purpose of an effector is to achieve an effect of a particular intensity. If this purpose is reached and the intensity maintained, it can be said that the effector is functioning in "constancy." As we shall see, this is most frequently the case in physiological effectors (fig. 2, *B*).

If the purpose of the effector is to achieve an effect of a maximum intensity, which is never reached and can even tend toward infinity, it is then said that the effector functions in "tendency" (fig. 2, *A*).

An effect can be "positive" or "negative." Similarly, the effector can be either

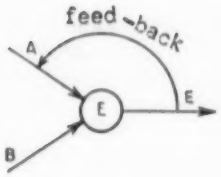

FIG. 1. Representation of effector, its effect, and its factors. (All illustrations are reprinted with permission from *Presse médicale*, Nov. 12 and Dec. 31, 1958.)

positive or negative, insofar as its variations influence the variations of the effect in the same or in the opposite direction.

A feedback can also be either positive or negative. An effector functioning in constancy is properly regulated if it is subjected to a negative feedback. In the opposite case it will lose its regulation.

Conversely, the effector functioning in tendency is under the influence of a positive feedback. In the organism, the tendency is generally limited to a certain value; the functioning of the kidney tubule cells is a good illustration of this.

In figure 1 it can be seen that the feedback, which originates from effect E, will influence the factor with a certain delay. Hysteresis results therefrom. Similarly, the modification introduced in factor A will be felt by E only with a certain delay, which is called the efficiency delay. These two concepts explain, for example, why an effector in constancy maintains its equilibrium around an ideal value, which is never stably reached, and why the effect goes through oscillating values. Here again we find the harmonious postaggressive oscillating reaction. We would now like to explain why we describe a disharmonious postaggressive oscillating reaction in physiopathology. The reason is that an effect can be produced only if the intensity of its factors remains within given limits.

An effect depends on many factors of variable intensity. It is a causative function. The limits of a causative function are formed by the ensemble of the values that can be assumed by all these variables without resulting in the interruption of the effect.

In physiopathology it can thus be assumed that the effect will not be produced if the eventual variations of the environment lead to variations of the intensity of certain factors forcing them outside of their limits. We shall see that if the variations of the environment force the factors responsible for the regulation of the equilibrium of a complex organism outside of their limits, the organism will alter its *modus operandi*.

APPLICATIONS TO PHYSIOLOGY

With the help of these extremely simplified notions, we must first try to discover

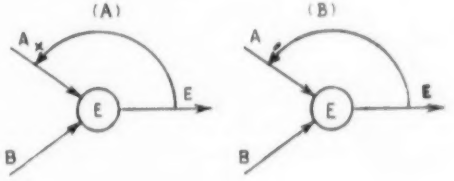

FIG. 2. *A*, Positive feedback; functioning in tendency. *B*, Negative feedback, functioning in constancy.

the nature of the finality of a living organism. Since the work of Claude Bernard, it has been repeated that the finality is the maintenance in the internal environment of the constancy of the conditions necessary for life, in other words, of Cannon's homeostasis. We must face the fact that this constancy disappears in physiopathology. It would be too time-consuming to explain here what leads us to accept that the maintenance of this constancy (which obviously calls into play autoregulated systems) is only the means to achieve the true finality. This finality is the maintenance of the degree of organization of the living matter in spite of and against the tendency toward leveling, toward entropy. To be accurate, the study of the cybernetic mechanisms that achieve it should therefore begin at the level of the protein molecule, then progress toward that of the unicellular organism. As far as we know, such a study has not yet been attempted. As far as we are concerned, we shall begin to apply these concepts at the cell level, and we shall accept that the first "finality" in a complex organism is the maintenance of the cell organization.

CELL AUTOREGULATION

We have previously described the mechanism of cell autoregulation.

When it functions under aerobic conditions, the cell as an effector can be schematically represented (fig. 3) as having for effects the liberation of H ions and of CO_2. The factors are represented by dehydrogenation and decarboxylation processes. The selector mechanism is represented by the membrane, which controls permeability.

The more the metabolism increases (dehydrogenations plus decarboxylations), the greater is the liberation of H ions and CO_2, and the more the membrane potential increases. This increase results in a proportional decrease of membrane permeability, leading then to a proportional decrease in membrane potential, and so on. This is a typical example of a constancy functioning.

PHYSIOLOGICAL ORGANIC AUTOREGULATION

The extracellular environment or the ratio of the concentrations in $BHCO_3$ and H_2CO_3 of this environment $\left(\frac{[BHCO_3]}{[H_2CO_3]}\right)$ may be taken arbitrarily as the effector, and the maintenance of the concentration in H ions may be taken as the purpose of this effector.

Under aerobic conditions, the factor that will cause a positive variation of this concentration is the liberation by the cell of H ions and CO_2. Figure 3 will therefore terminate at the next effector, "the extracellular environment," and the effect of this cell will become the positive factor on the extracellular environment. The

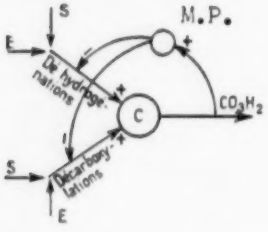

FIG. 3. Cell autoregulation functioning under aerobic conditions. C = cell; M.P. = membrane potential; S = substrates; E = enzymes.

effect selected for this latter will be its H_2CO_3 concentration (fig. 4). When it increases, the cell membrane becomes depolarized. We shall, therefore, draw a negative feedback starting from this effect and leading to the membrane potential. We have seen, however, that membrane polarization acts negatively on metabolic intensity. Two negative actions result in a positive one. The increase of the H ion concentration—acidosis—as long as it remains within physiological limits, will increase metabolism; a positive feedback is involved, and therefore the system will function in tendency. If one or more negative factors did not permit equilibration of the H_2CO_3 concentration of extracellular fluids under constancy conditions, the cell organization would be very rapidly destroyed since we have just seen that the maintenance of this organization is possible only under constancy conditions. This results from the fact that in figure 3 we have selected as the effect on the cell effector the amount of H_2CO_3 liberated and that in figure 4 we have taken as the effect on the extracellular environment effector its H_2CO_3 concentration. We have progressed from the cell level to that of the organism.

The negative factors are the kidneys and the lungs, which assure the evacuation of CO_2 and H ions outside of the organism. The functioning of the kidney can be schematically represented. For simplicity's sake we shall limit ourselves to only one of its H ion excretion mechanisms (fig. 5).

It is known that the cell tubule can produce H_2CO_3 from CO_2 and the H_2O of the plasma through the action of the carbonic anhydrase. The H_2CO_3 traps the sodium filtrated at the level of the glomeruli and forms $NaHCO_3$, which then returns into the circulation. The H ion is then liberated into the urine. This mechanism can be represented as in figure 6.

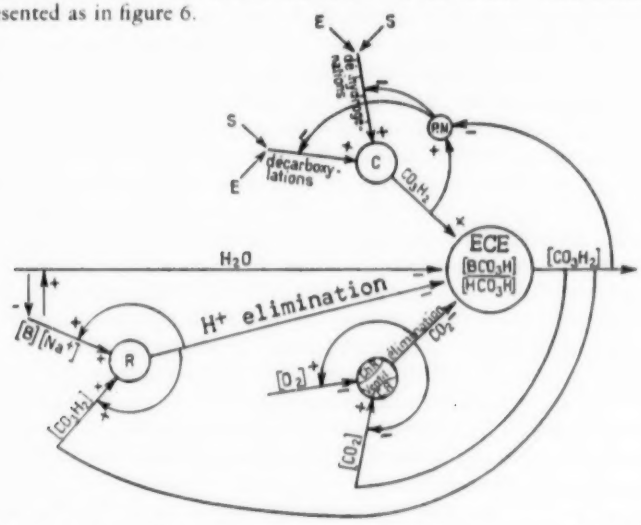

FIG. 4. Effect on the extracellular environment effector of its H_2CO_3 concentration. C = cells; E = enzymes; S = substrates; P.M. = membrane potential; ECE = extracellular environment; R = kidney tubule cell; Ventil. = ventilation; ChR = chemoreceptors; C.R = respiratory centers.

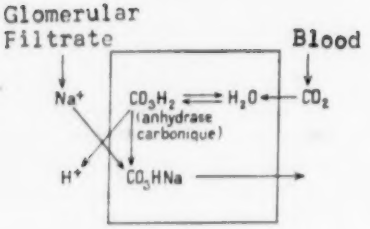

FIG. 5

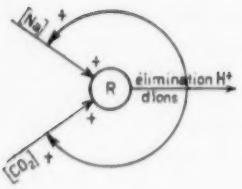

FIG. 6

FIG. 5. H ion excretion mechanism of the kidney.
FIG. 6. Mechanism of liberation of the H ion into the urine.

A positive feedback—a functioning in tendency—is therefore involved, which will lead to reintegration into the organism of that much more CO_2 and Na so that there will be more H ion excreted in the urine. Conversely, the more the plasma concentration of CO_2 and Na increases, the more H ions will be excreted (combined with strong anions), but the greater also will be the CO_2 and Na retention. This mechanism can be limited only by parallel lowering of the H ion concentration in the organism. We shall see later in a few examples that this hypothetical representation is supported by facts that are thereby clarified.

It should be noticed that the more sodium is retained, the more water is also retained. An "interaction" between two factors acting on the "extracellular environment" effector therefore exists since the more water is retained the more the H_2CO_3 concentration of the extracellular fluid is decreased. This leads to a greater decrease of the CO_2 and Na concentrations. A third negative factor should, therefore, be added to the regulations of the H_2CO_3 concentration of the extracellular fluid: the extracellular water. Its regulation will be considered later.

In the lungs (fig. 4) the ventilation can be taken as the effector, and it is controlled by the respiratory center (CR)—particularly sensitive to the blood CO_2 concentration (CO_2)—and the chemoreceptors (ChR)—particularly sensitive to the blood O_2 concentration (O_2) (fig. 4). The higher the O_2 concentration, the more the chemoreceptors are inhibited. This is a negative factor on the ventilation. On the contrary, the more the CO_2 concentration increases, the more the respiratory centers will be stimulated (it is understood that this holds true under physiological conditions, that is to say, when the variable factors remain within certain given limits), and this is a positive factor on the ventilation. When ventilation increases, more CO_2 is excreted and less is found in the blood: a negative feedback on a positive factor; thus there exists a functioning in constancy, which maintains the equilibrium of the effect. Similarly, when the ventilation increases, the oxygenation improves; now a positive feedback on a negative factor on the ventilation is involved; therefore, here also the functioning is in constancy.

Let us observe in passing some facts made obvious by this cybernetic representation. Let us suppose, for example, that the excitability of the respiratory centers is depressed by an anesthetic, and that our patient is made to breathe a gas mixture rich in oxygen. It is obvious that if the positive factor on ventilation is absent or

inadequate, the increase of the value of the negative factors will lead only to a deeper depression of respiration, whereas when the respiratory centers are intact, the respiratory depression that could result from the increase of oxygen concentration of the inspired air is immediately compensated by the increase of the pCO_2. An opposite line of reasoning can be followed when the decrease in the partial pressure of the oxygen in the inspired air is concerned. If it causes a hyperventilation, it will lower the CO_2 and depress the activity of the respiratory centers. Since these centers are comparatively more sensitive, anoxic anoxia causes but little ventilatory compensation.

It can, therefore, be seen that the equilibrium in the concentration of CO_2 of the extracellular fluid can be expressed as the maintenance of the equilibrium between the cell production of H_2CO_3 on the one hand—a positive factor—and as the excretion of CO_2 by the lungs and of H ions by the kidneys on the other hand—both negative factors. The water concentration, which is related to that of sodium and therefore of CO_2, is also a negative factor acting on the H_2CO_3 concentration.

It should finally be added that the positive feedback that regulates the effect, i.e., the liberation of H ions and CO_2 by the tissues and their excretion out of the organism by the emunctories, originates from this same effect. Indeed, this is because the organs responsible for the excretion of the H ions and CO_2 are also formed by cells, the metabolism of which is autoregulated and involves the same mechanism found in other tissues. The increase of H_2CO_3 concentration in the extracellular environment results in an increase of ventilation. Such is the case, for instance, in muscular exertion because it depolarizes membranes and renders them more permeable, increases cell metabolism through a positive feed-back mechanism, and increases simultaneously the work of the cardiovascular and renal systems. The neurones of the respiratory centers become depolarized and therefore stimulated, and ventilation is increased. A positive feedback on a negative factor is involved at the level of most tissues and leads to a functioning in tendency that perpetuates the disturbances. But a positive feedback on negative factors is involved at the level of the organs mobilizing and excreting the H ions and CO_2 and leads therefore to a functioning in constancy and to a correction of the disturbances.

Let us consider now as the effect of the extracellular environment its sodium concentration (Na^+). It can be expressed as osmotic pressure (fig. 7) if we agree to overlook temporarily the other elements that enter into play in establishing its value. The sodium concentration has a positive factor, which is the amount of sodium contained in the extracellular fluid, and a negative factor, which is the amount of water present in this same environment (fig. 7). It is admitted that the over-all value of these two factors depends on the secretion of aldosterone by the adrenals. Indeed aldosterone is responsible for water and sodium retention. This retention, however, inhibits the aldosterone secretion. This is a negative feedback and a functioning in constancy that probably bring into play the still much debated volume receptors.

Osmotic pressure (Na^+), however, acts negatively on the osmoreceptors, which are stimulated by dilution. These osmoreceptors act on the posterior lobe of the pituitary to inhibit it, and again a negative action is involved. The pituitary secretes

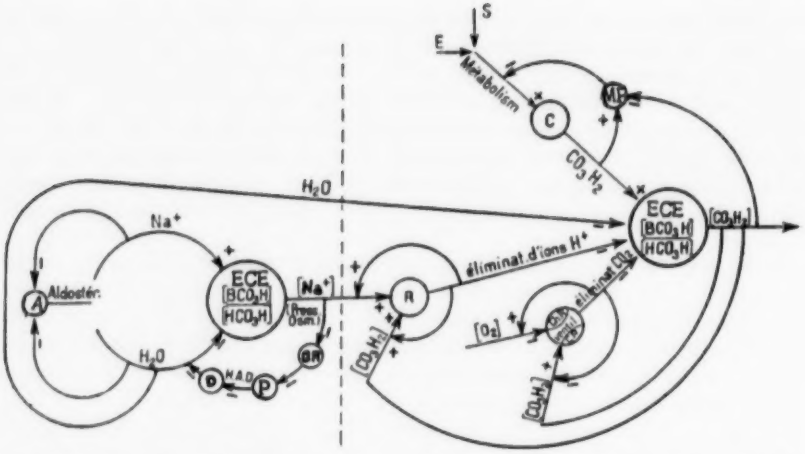

FIG. 7. Osmotic pressure. A = adrenals; ECE = extracellular environment; O.R = osmoreceptors; P = pituitary; D = diuresis; H.A.D. = antidiuretic hormone; R = kidney; ventil. = ventilation; Ch.R. = chemoreceptors; C.R. = respiratory centers; Press. Osm. = osmotic pressure; C = cell; MP = membrane potential; Aldostér. = aldosterone.

an antidiuretic hormone, which also acts negatively on diuresis, and in turn, finally acts negatively on the amount of water in the extracellular environment. A positive feedback on a negative factor is, therefore, involved leading to the functioning in constancy of the osmotic pressure (Na^+).

The illustrations can now be combined by using the osmotic pressure in figure 7 (since we have stated that we identified it with Na^+) as the factor of the H^+ elimination at the level of the kidney tubule cell, and by taking as the origin of the H_2O negative factor of figure 4 the H_2O factor of figure 7 (fig. 7).

HOW TO APPLY THE PRECEDING CONCEPTS

First, it appears that all living phenomena under physiological conditions can be summarized as the conversion within the cell of H molecules bound to the substrates supplied by diet into H ions and electrons accepted by oxygen. These are then carried to the emunctories and excreted. Another observation that must be made is that the transfer of hydrogen through the organism leads to a relative sparing of "bases," in particular of sodium and of water, since the more the kidney excretes H ions, the more it retains sodium and water. This phenomenon, however, will depress aldosterone secretion. Consequently, the quantitative water and salt homeostasis will be restored.

Moreover, this representation seems to bring to light certain correlations between *p*H and osmotic pressure, which at first sight would not be quite evident. Indeed, the tendency to acidosis will be accompanied by sodium retention and the osmotic pressure will rise. The positive feedback that acts through the osmoreceptors will

lead to water retention. Since the total amount of water and sodium will rise, the secretion of aldosterone will be depressed and the osmotic pressure controlled. Conversely, metabolic alkalosis will be regulated, on the one hand, by ventilation that will be depressed and, on the other, by the decrease of the H ion and the increase of bicarbonates excreted in the urine. Since the osmotic pressure decreases, the stimulation of the osmoreceptor will increase diuresis and osmotic pressure will again be controlled.

The most interesting fact, however, concerns the mechanism of the disturbances that are likely to appear if an organism is maintained under constant ventilation. By suppressing one of the main regulating systems of the H_2CO_3 concentration of the extracellular fluid, the equilibrium can be maintained only if the metabolic intensity remains adapted to this stable ventilation. Starting from this type of equilibrium, which can be set initially, the diagram will show that if cell metabolism is disturbed by any type of pharmacological means, the organism cannot function any more in "constancy" but only in "tendency" and that a metabolic disturbance will amplify itself very rapidly through a positive feedback. This concept seems to us to be of major importance. Indeed, we feel that it is not an exaggeration to state that all of pharmacology must be studied again under constant ventilation since, on an animal under equilibrium, the introduction into the organism of a pharmacological agent will be accompanied by a rapidly dampened oscillating reaction if the disturbance that the agent causes on cell metabolism does not go beyond the limits within which autoregulation remains possible. The main metabolic cell disturbance will thus be hidden, whereas constant ventilation will cause its progressive amplification even when small doses are used. According to this same principle, ligature of the ureters can also furnish useful information.

This schematic representation is obviously extremely simplified in order not to overcomplicate from the start the description of the application to physiology of the cybernetic representation. Innumerable effects, effectors, factors, and feedbacks, the importance of which cannot be underestimated, have not been taken into consideration. In this schematic representation, we have not attempted to integrate endocrine regulation mechanisms or, for instance, the cardiovascular system, the role of which is considerable in the regulation of the equilibrium of the H ion of the extracellular environment. On the basis of the preceding findings, nothing prevents their integration. We have studied this with profitable results, but the presentation of such an integration cannot be included into an introductory article. It seems more useful to demonstrate how these principles can be put to best advantage.

APPLICATION TO PHYSIOPATHOLOGY

It was previously mentioned that an effect can be produced only if the intensity of the factors remains within certain limits. This is true in physiology where hysteresis is responsible for the oscillating nature of the reaction that remains harmonious. The intensity of these factors depends on the environment, and it is obvious that the maintenance of the physiological state is possible only within certain narrow limits of variations of this environment. At the metabolic level, the

physiological state is accompanied by aerobic respiratory processes. When the variations of the environment go beyond the limits within which the factors can give rise to effects that control the variations of these factors through a feed-back mechanism, experience proves that the organism can still recover its equilibrium. But experience has taught us also that, in such cases, the autoregulated mechanisms that are called into play are not those that assure the maintenance of this equilibrium under physiological conditions. Physiological feedbacks are indeed unable to maintain the factors within their limits. Identical observations are very well known in cybernetic machines. In such a case the machine must switch from one type of *modus operandi* to another. The living machine does the same thing but one point must be made clear. A change in the *modus operandi* involves the means since the finality remains unchanged. This is the same finality mentioned previously: the maintenance of the degree of organization of the living matter. Under physiological conditions the means used to maintain this degree of organization is the maintenance of the constancy of the internal environment. Under physiopathological conditions, however, biological observations have long demonstrated that this constancy is not immediately restored: the reaction becomes disharmonious. The new temporary *modus operandi* uses flight or struggle to achieve finality. Stable splanchnic and cutaneous vasoconstrictions, acidosis, hemoconcentration, hyperglycemia, hepatic and renal anoxias leading to hyperammoniemia and anuria, etc., confirm the temporary departure of the organism from the over-all homeostasis to favor the maintenance of this homeostasis at the level of certain privileged areas, which make possible flight or struggle: nervous system, heart, lungs, and muscles. If this change in *modus operandi* permits the individual to flee or suppress the aggression imposed by the environment in a short enough time so that the disfavored organs do not suffer irreversibly, the finality of the organism—that is to say, the maintenance of its degree of organization—is thereby achieved. The return to homeostatic equilibrium will take place more or less rapidly, but if not, immediate or delayed death will result.

What is the purpose that should be selected to define the new *modus operandi* followed by the organism to assure its finality under these abnormal environmental conditions? Observations show that the maintenance of the constancy of the H ion concentration in the extracellular fluid is not the purpose sought to assure this finality. On the contrary, the hypoxia consecutive to the local circulatory changes leads to an anaerobic form of life more or less marked at the level of certain organs; this leads to an increase of glycolytic processes at the expense of respiratory processes and to the liberation by these organs of strong acids more dissociated than H_2CO_3. But these "strong" acids should be excreted by the kidneys; however, their vascularization is interfered with and diuresis stopped.

The only purpose that seems logical is the intensity of the energy liberated by the organs that assure freedom of motion with respect to the environment. It is indeed this energy liberation that, through the flight or struggle it permits, preserves the finality—the maintenance of the organization of living matter—by avoiding or suppressing the aggression, i.e., the contingent cause that forced the factors outside of their limits. In such a case, it is conceivable that organs, such as the kidneys, that

control negative factors of the H ion concentration of the extracellular environment have their functioning inhibited. It can also be understood that the organism will not function in constancy but in tendency so long as the disappearance of the contingent cause responsible for the switch in *modus operandi* is not eliminated. The energy liberated by the organs assuring autokinesis will increase progressively as long as the abnormal factor keeps on acting and total depolarization is not achieved.

The role that training can play in many borderline cases can finally be understood. The result of training will be indeed to broaden the limits of the variables, to widen their boundaries, without *ipso facto* causing a cessation of the effect and necessitating a change in the *modus operandi*.

Ammonia metabolism can be taken as a typical cybernetic representation of physiopathological phenomena (fig. 8).

In the organism under physiological conditions, ammonia metabolism appears as of secondary importance since the healthy liver can metabolize intestinal ammonia and the exogenous supply of carbohydrates can assume an essential part of cell metabolic expenses. Thus the H_2CO_3 concentration of the extracellular environment is easily maintained.

As soon as the organism must have recourse to lipids, proteins, and neoglucogenesis to ensure its energy supply, the metabolism leads to the formation of organic acids

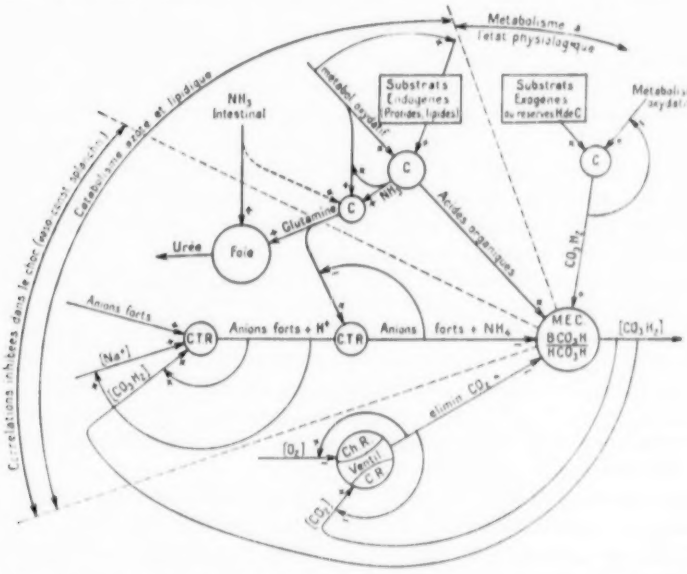

FIG. 8. Ammonia metabolism. Anions forts = strong anions; Catabolisme azoté et lipidique = nitrogen and lipid catabolism; Correlations inhibées dans le choc (vaso-const. splanchn.) = correlations inhibited in shock (splanchnic vasoconstriction); Métabolisme à l'état physiologique = metabolism under physiological conditions; Substrats Endogènes (Protides, lipides) = endogenous substrates (proteins, lipids); Substrats Exogènes ou reserves H. de C. = exogenous substrates or carbohydrate reserves.

and ammonia, as can be seen in fasting. The liver and muscle glycogen reserves are practically exhausted after 12 hours of fasting. This is also observed after vomiting, anesthesia, febrile conditions, and thyrotoxicosis. Oxidative metabolism is frequently disturbed here and leads to a worsening of the acidosis. In diabetes, finally, the inability to utilize carbohydrates is at the origin of the acidosis.

In summary, these cases are characterized by nitrogen and lipid catabolism, caused by the lack of carbohydrates or the inability to utilize them in the oxidative cycle.

The overproduction of NH_3 by the cell will induce an overproduction of glutamic acid to convert NH_3 into glutamine and thus detoxify it. The increase demand in glutamic acid is associated with an increase demand in α ketoglutaric acid and consequently with a speeding up of all the steps in the tricarboxylic acid cycle. The oxidative metabolism is thus suddenly increased. But it can be increased only at the expense of endogenous substrates resulting in an increase of protein catabolism and of NH_3 formation. The cell works thus in tendency and no longer in constancy. The exhaustion of the tricarboxylic acid cycle may take place, and at the level of the central neurons it would then be manifested by coma, according to Bessman. It is only when the tricarboxylic acid cycle proves to be unable to perform the NH_3 transamination into glutamine that ammoniemia increases. Hyperammoniemia appears, therefore, above all as a sign of deep disturbances of the oxidative metabolism.

Glutamine will be carried to the liver and the kidneys, assuming in this case that they function normally. In the liver, the ornithine cycle will lead to the formation of citrulline and urea. In the kidney, strong anions will be excreted to compensate for the liberation by the cell of organic acids, which have replaced HCO_3 in the ratio: $\frac{BHCO_3}{HHCO_3}$.

The CO_2 will be excreted by the lungs and the Na reabsorbed by the tubule cells in exchange of an H ion. As is well known, the latter will combine with a strong anion to yield a strong acid, which, in turn, will form an ammonia salt at the level of the tubule cells by taking away NH_3 from glutamine.

The blood returning to the liver after passing through the kidney will contain that much less glutamine so that there will be more strong acids to excrete to compensate for the acidosis resulting from the liberation of organic acids by the cells. The liver will have that much less material available to synthesize urea, all other factors remaining unchanged as far as the intestinal NH_3 is concerned. The coefficient of ureagenetic deficiency thus evolves around an essential function, that of the maintenance of the acid-base balance. In such cases, hypochloremic types of acidosis are observed.

In all cases it can be well understood that it is important to give a massive carbohydrate supply capable of limiting maximally the nitrogen catabolism, which generates NH_3 and organic acids. Insulin will facilitate carbohydrate intermediary metabolism.

If the hepatic function is seriously disturbed (as in cirrhosis, hepatitis, vena cava–portal anastomosis), the excretion of NH_3 will rest only on kidney function and the excretion of strong acids. In such a case again, it is urgent to prevent the nitrogen catabolism and to limit the formation of intestinal NH_3. The considerable danger of

certain therapeutic agents, such as carbonic anhydrase inhibitors (acetazolamide), can be understood. They favor bicarbonate loss by the kidney, hinder the excretion of strong acids, and make the acidosis and thus nitrogen catabolism even worse. But above all, because they limit NH_3 renal excretion, they force the cell to speed up metabolism, which rapidly ends in exhaustion and coma.

The liver and the kidneys can both be damaged. Moreover, the vasomotor reaction to various aggressions is always accompanied by splanchnic vasoconstriction and by the functional inhibition of these organs: the situation is no longer chronic but becomes acutely pathological as observed in the various shock states as well as in burns. The acid-base balance can no longer be maintained except by ventilation, therefore very unsatisfactorily and temporarily. Cell metabolism then will function in tendency since it is practically under the influence of only a positive feedback. The change in the *modus operandi* (flight or struggle) must rapidly comply with the organic finality, otherwise death by exhaustion will be rapid. Here again, the importance of a massive glucose supply as well as of the suppression of the splanchnic vasoconstriction by neuroplegia is obvious. It also becomes clear that it is important to sterilize the intestine with antibiotics since the flora of the intestine generates NH_3, which the anoxic liver cannot detoxify.* The entire classical postoperative nitrogen catabolism is condensed here, since the adrenergic system and the pituitary-adrenal axis play an essential correlation role between splanchnic vasoconstriction and cell nitrogen catabolism.

In all the cases cited, provided that the intensity and the duration of the aggression as well as the seriousness of the lesions are controlled, it is possible to understand the importance of an imposed restoration of homeostasis and, in the first place, of circulatory homeostasis (suppression of the vasoconstriction, which has become useless and is a factor of metabolic acidosis). The flight or the struggle has lost its meaning and the switch in *modus operandi* is no longer necessary. Similarly, it is possible to understand the importance of maintaining the balance between formation and excretion of H ions and CO_2 and in some cases, therefore, of decreasing the metabolic intensity by cold when the mobilization and excretion of H ions and CO_2 are threatened. Neuroplegia and artificial hibernation, accordingly, find some additional supporting arguments. If the restoration of homeostasis is imposed, however, the physiological *modus operandi* must be preserved, and vice versa. Thus, in cases of hemorrhage, a neuroplegia without restoration of the blood mass is as illogical as a transfusion without neuroplegia.

This is all merely a more or less hypothetical and simple interpretation of facts. Cybernéticians have taught us the importance of "models" in the understanding of a complex mechanism. The change in *modus operandi* that we have just described in the complex organism, passing from physiology to pathology, is illustrated by Ashby's homeostasis. When a particular determinism does not allow the obtaining of the effect of its finality, the latter will reorganize its *modus operandi* and seek new equilibrium conditions.

* We observed that the hyperammoniemia that is associated with the shock episode in severe burns is brought back to normal by plain neuroplegia.

CONCLUSIONS

This very schematic synopsis is intended only to draw the attention of the physician and the biologist to the possibilities offered by cybernetic representation and method of reasoning, and we have demonstrated that this method can help us: (1) set down correctly and diagrammatically the data of a problem in order to arrive at its solution clearly; (2) integrate and thus correlate factors the complexity of which often renders a synthesis difficult, and follow in a simple fashion their more or less far-reaching consequences; (3) bring to light certain facts and the importance of certain experimental protocols; (4) define and satisfy better the internal finality of complex organisms such as the human body.

We hope that this unavoidably fragmentary first attempt will incite those interested in this field to develop the method. It seems evident that it could help considerably in the understanding of the extremely complex autoregulated mechanisms that assure the maintenance of the organization of living entities in the midst of variations of environmental contingencies.

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Highlights of the 18th Veterans Administration-Armed Forces Conference on the Chemotherapy of Tuberculosis

James W. Raleigh, M.D.

SECRETARY, VETERANS ADMINISTRATION-ARMED FORCES COMMITTEE ON THE CHEMOTHERAPY OF TUBERCULOSIS, VETERANS ADMINISTRATION, TUBERCULOSIS SERVICE (115A)
WASHINGTON, D. C.

The 18th Veterans Administration-Armed Forces Conference on the Chemotherapy of Tuberculosis was held in St. Louis Feb. 2–5, 1959. Registration exceeded 400 with representatives from Brazil, Canada, Germany, Great Britain, Honduras, Japan, and the Republic of the Philippines and from 38 states and the District of Columbia.

Reports were presented on cooperative studies of the treatment of pulmonary tuberculosis, tuberculous pleurisy with effusion, and tuberculosis of the genitourinary tract. In addition, individual reports on other aspects of the diagnosis, laboratory study, and treatment of tuberculosis, coccidioidomycosis, and pulmonary infection due to atypical mycobacteria were presented. Evening meetings of the committees representing Veterans Administration-Armed Forces Cooperative Studies on Histoplasmosis, Coccidioidomycosis, Blastomycosis, and Tuberculosis in Neuropsychiatric Hospitals were held and their findings reported to the conference at large.

COOPERATIVE STUDIES

Three Drugs Versus Two. Comparisons were reported of the therapeutic effectiveness of daily streptomycin-isoniazid, isoniazid–para-aminosalicylic acid, and daily streptomycin–para-aminosalicylic acid–isoniazid in 1150 patients with previously untreated cavitary pulmonary tuberculosis. After four and eight months of therapy, no significant difference in the effectiveness of these three regimens was noted with respect to roentgenographic improvement, cavity closure, conversion of sputum by culture, and the emergence of drug-resistant tubercle bacilli. Toxic reactions to each drug occurred with equal frequency on all three regimens, but by simple addition, the total incidence of drug reactions was greater on the triple-drug regimen.

Of the 793 patients in the study whose treatment included streptomycin, 220 were assigned to a subsidiary study comparing the toxic effects of streptomycin sulfate versus streptomycin pantothenate on the eighth cranial nerve. The study, using the double-blind technique, measured the incidence of vertigo, ataxia, response to caloric stimulation, tinnitus, and hearing loss and revealed no significant difference in this respect from the two streptomycin preparations.

A report from the National Jewish Hospital in Denver stressed the importance of even partial resistance to as little as 2.5 μg./ml. of streptomycin and 0.2 μg./ml. of isoniazid as a cause of treatment failure. Results reported by the Denver group seem to support this notion although their study lacked controls.

Isoniazid Alone Versus Isoniazid–Para-aminosalicylic Acid. Comparisons of the therapeutic effectiveness of isoniazid alone with isoniazid–para-aminosalicylic acid in 280 patients with minimal and moderately advanced noncavitary pulmonary tuberculosis were reported. There was no significant difference in the effectiveness of these two regimens and only a faint hint that isoniazid resistance and roentgenographic worsening during therapy might be somewhat more frequent with isoniazid alone. Untoward drug reactions during treatment occurred in 14 per cent of the patients treated with isoniazid–para-aminosalicylic acid and required interruption of treatment in 10 per cent. Most of these reactions were due to para-aminosalicylic acid.

Cycloserine-Isoniazid. A comparison was reported of the effectiveness and toxicity of isoniazid–para-aminosalicylic acid and isoniazid-cycloserine, 0.5 Gm./daily, in 732 patients with previously untreated cavitary pulmonary tuberculosis. With respect to roentgenographic improvement, cavity closure, and conversion of sputum by culture, no difference in the effectiveness of the two regimens was noted. A somewhat higher incidence of isoniazid-resistant tubercle bacilli emerged in the isoniazid-cycloserine group in the patients with large cavities. Toxicity with isoniazid-cycloserine, 0.5 Gm. daily, was less than with the other regimen, para-aminosalicylic acid intolerance constituting the major manifestation of this in the latter regimen.

A report from Chicago suggests that under certain circumstances, the toxic effects of high dosages of cycloserine on the central nervous system can be controlled, if not prevented, by concomitant administration of sedatives, anticonvulsants, ataractic agents, and pyridoxine, singly or in combination. Of 50 patients believed to be at the end of their therapeutic resources prior to treatment with cycloserine in a dosage of 1.0 to 2.5 Gm. (25 to 44 mg./Kg.) daily, all but 10 were able to complete the planned course of cycloserine therapy. Thirty-one became acceptable candidates for surgical treatment and 20 achieved an inactive classification, while 8 more were significantly improved.

Isoniazid-Pyrazinamide. A comparison of the effectiveness and toxicity of isoniazid-pyrazinamide, 1.5 Gm. daily, with isoniazid–para-aminosalicylic acid, 12.0 Gm. daily, in 269 patients with previously untreated cavitary pulmonary tuberculosis was reported. In less advanced cases, the two regimens were therapeutically equivalent; in more advanced cases with a larger cavity and with multiple cavities, isoniazid-pyrazinamide appeared less effective.

The frequency of untoward reactions during drug therapy was similar in the two regimens; those occurring in the isoniazid-pyrazinamide–treated patients were of much greater consequence, with 1 death from acute yellow atrophy of the liver and several instances of hepatic dysfunction. The reactions in those receiving isoniazid–para-aminosalicylic acid were mainly gastrointestinal symptoms and hypersensitivity reactions.

High-Dosage Isoniazid. Comparisons were reported of daily streptomycin plus isoniazid, 1200 mg. daily, with the three drug regimens in general use (cf. supra) in the treatment of 317 patients with previously untreated cavitary pulmonary tuberculosis. There was no statistically significant difference in the effectiveness of these

four regimens. When the patients on all four regimens were divided according to results of serum isoniazid bioassay into "rapid inactivators" or "slow inactivators," it appeared that the slow inactivators fared slightly better with respect to sputum conversion than rapid inactivators regardless of the regimen they received. Superiority of isoniazid, 1200 mg. daily, over isoniazid, 300 mg. daily, in either rapid or slow inactivators of isoniazid was not demonstrated in this study.

From Salt Lake City, Utah, came an interesting report on the genetic aspects of isoniazid inactivation. The isoniazid inactivation patterns were studied in 20 families comprising 40 parents and 79 children. From these data, it was concluded that the isoniazid inactivation pattern is a hereditary trait, that it is not sex-linked, that rapid inactivation is probably inherited as a Mendelian dominant, and that slow inactivation is probably inherited as a simple Mendelian recessive.

Thiocarbanidin. A preliminary report on 72 patients treated for two to eight months indicates that thiocarbanidin in combination with either streptomycin or isoniazid is well tolerated in dosages of 1.0 Gm. daily but does not delay the emergence of isoniazid- and streptomycin-resistant tubercle bacilli as well as para-aminosalicylic acid does in either original or re-treatment drug-susceptible cases. It is postulated that poor absorption of thiocarbanidin from the gastrointestinal tract is responsible for this, and efforts to improve its absorption are under study.

A similar study of thiocarbanidin in a dosage of 2.0 Gm. daily with isoniazid was reported from Washington, D. C. In 41 patients treated for 3 to 12 months, no thiocarbanidin intolerance or toxicity was observed. Sputum conversion occurred in 20 patients. In the 21 who did not convert, isoniazid-resistant tubercle bacilli were recovered in 15 (71 per cent) associated in 4 patients with unfavorable clinical or roentgenographic change. Thiocarbanidin-resistant tubercle bacilli were not observed.

Kanamycin. The therapeutic effectiveness and toxicity of kanamycin were studied in 75 patients with advanced cavitary disease and whose organisms were resistant to streptomycin and isoniazid. Therapeutic effectiveness could not be assessed since 65 of the 75 patients admitted to the study were lost prematurely: 29 due to auditory toxicity, 8 due to irregular discharge, 5 due to pain at the injection site, 3 due to roentgenographic worsening, 3 due to death from tuberculosis, and the remainder for miscellaneous reasons. Although renal toxicity manifested by proteinuria and/or cylindruria was frequently observed, it was listed as the reason for discontinuation of therapy only twice. Sputum conversion by culture was rare, and while resistance to kanamycin was observed frequently, it occurred less often in those patients receiving para-aminosalicylic acid or tetracycline with kanamycin than when kanamycin was given alone.

A report from New York City confirmed the eighth nerve toxicity of kanamycin and the emergence of kanamycin-resistant organisms but noted more favorable results than the Veterans Administration study, particularly in more acutely ill patients. Sputum conversion by culture occurred in about one third, kanamycin resistance was frequent in those remaining positive, and hearing loss was frequent when kanamycin was given in dosages of 1.0 Gm. daily or more. Studies of kanamycin, 1.0 Gm. three times weekly, with para-aminosalicylic acid are in progress

in hopes that the more favorable experience of the Japanese investigators will be duplicated.

THORACIC SURGERY

From Chicago were reported the results of 75 pneumonectomies with an operative mortality of 2.5 per cent and a complication (empyema) rate of 5 per cent. Of the 73 survivors, 70 were discharged from the hospital, 39 (56 per cent) with consistently negative sputum. The second report, from Sunmount, N. Y., concerned 14 patients who had pneumonectomies performed in the presence of a contralateral cavity. Eight of the 14 were inactive on follow-up 14 to 29 months postoperatively and 2 others were negative when lost to follow-up shortly after operation. Two operative deaths and 1 late death (22 months postoperatively) occurred. One other patient still has active disease.

A high complication rate in resection for pulmonary disease caused by atypical mycobacteria was reported from one center. This was attributed to unusually extensive (compared to tuberculosis) involvement of the bronchial tree found in the resected specimens from these cases. Another center further south had neither the complication rate nor the extensive disease in the bronchial tree. It is not at all certain that the two institutions were dealing with the same species of atypical mycobacteria.

EXTRAPULMONARY TUBERCULOSIS

Pleurisy with Effusion. A follow-up report was presented on 400 patients diagnosed as having tuberculous pleurisy with effusion (although only 15 per cent were bacteriologically confirmed as tuberculous). No antimicrobial therapy was given to 138 patients, and antituberculous chemotherapy was given to 262 patients, 114 receiving a chemotherapeutic regimen containing isoniazid and 148 receiving chemotherapy that did not include isoniazid. The specific drug regimen and its duration were not controlled, and inter-regimen comparisons were not attempted. It was found, however, in this five-year follow-up study that tuberculous complications developed in 23 per cent of the untreated group and in 10 per cent of the treated group, and when the latter is subdivided, complications developed in 4 per cent of the isoniazid-treated group and in 12 per cent of the nonisoniazid-treated group. Pulmonary tuberculosis was the most frequent complication encountered in both treated and untreated groups.

Miliary and Meningeal. No data from the cooperative study were reported, but a report was made from a Chicago group on the treatment of 71 patients with tuberculosis meningitis alternately assigned to one of the following regimens: (1) isoniazid alone, 8 to 10 mg./Kg. daily, 22 patients; (2) isoniazid, 8 to 10 mg./Kg. daily, plus streptomycin (intramuscularly and intrathecally), 21 patients; (3) triple-drug regimen, streptomycin given only intramuscularly, 14 patients; (4) same as no. 3 plus hydrocortisone and ACTH, 14 patients. There were no significant differences in results that could be attributed to the drug regimen used or to the use of steroids. Better correlations were noted between response to therapy and age (poor response in those less than 2 years of age on all regimens, 70 per cent survival in the older

patients), race (poorer response in Caucasian than in non-Caucasian patients), and condition at the time of admission.

Genitourinary Tuberculosis. Two reports were presented: One dealt with the incidence of relapse in 183 patients who had successfully completed not less than one year of chemotherapy for genitourinary tuberculosis and who were followed up to three years after completion of this therapy. It was found, using life table methods, that one year after successful completion of therapy 9 per cent had relapsed; after two years 20 per cent had relapsed; and after 3 years 26 per cent had relapsed. Although relapse was based on bacteriological findings alone, in almost every instance the patient was re-treated, suggesting that the physician in charge regarded these patients as having relapsed.

The second report on genitourinary tuberculosis concerned the results of a series of patients treated with various regimens, again showing the more favorable results obtained in those patients treated with isoniazid–para-aminosalicylic acid and triple-drug regimens as compared to streptomycin alone or streptomycin–para-aminosalicylic acid. The introduction of new regimens including kanamycin, thiocarbanidin, and isoniazid will be watched with interest from the point of view of both efficacy and toxicity.

An interesting additional study was reported indicating that the children of patients with genitourinary tuberculosis react to tuberculin three times as frequently as would be expected. In addition, all of the positive tuberculin reactors were in the families of only 28 per cent of the parents with genitourinary tuberculosis. It was concluded therefore that genitourinary tuberculosis is communicable to household contacts and that awareness of this and the institution of reasonable hygienic measures are needed to prevent household contagion.

MISCELLANEOUS

Steroid Therapy. A controlled study on the effect of ACTH on the results of treatment when added to standard drug regimens in previously untreated pulmonary tuberculosis was reported from Brooklyn, New York. It was concluded that in addition to the expected rapid clinical response (defervesence and weight gain), the steroid-treated patients showed more marked roentgenographic improvement at four and eight months of therapy than did the controls. Differences in sputum conversion and cavity closure were less significant. Distinctive differences in the morphological appearance of lung tissue resected after (some months after, actually) steroid therapy were looked for but not found.

A study of tri-iodothyronine therapy in pulmonary tuberculosis in Philadelphia failed to demonstrate the favorable effects in human patients made thyrotoxic with this hormone that Lurie had shown in rabbits.

Air-borne Infection. An extension of the Baltimore study on air-borne infection was presented. By comparing "drug-susceptibility patterns" of organisms recovered from guinea pigs with drug-susceptibility patterns of patients in the experimental ward at the time air-borne infection was believed to have taken place, it was possible to determine that 19 of 22 guinea pigs infected over a two-year period could

be traced to just 2 of 62 patients. The similarity of this finding to that of the genitourinary tuberculosis study in which all the children reacting to tuberculin were found among the household contacts of only 28 per cent of the adult genitourinary tuberculosis patients surveyed is interesting.

Streptovaricin. A report on the use of streptovaricin in dosages of 5 and 10 Gm. daily indicates that with persuasion this dosage could be tolerated by the majority of patients and caused no serious side effects. Gastrointestinal disturbances of a minor nature were seen in most patients and a hypersensitivity reaction occurred in 1. The therapeutic results with these larger dosages in previously untreated patients were not impressive but in the opinion of the authors were better than would have been expected with semiambulatory hospital treatment alone. No definite differences in efficacy were noted between the patients treated with 5 Gm. daily and those treated with 10 Gm. daily.

Coccidioidomycosis. A study from San Fernando, California, indicates that in vitro susceptibility of *Coccidioides immitis* to amphotericin B varies with the type of cell used for the test. Vegetative cells from many strains were resistant to the drug, while arthrospores and spherules with their endospores from the same strains were susceptible to 1.0 μg./ml. The author stated that strains inhibited by 1.0 μg./ml. should be considered susceptible, those that grow in 1.0 but not in 5.0 μg./ml. are "potentially resistant," and those that grow in 5.0 μg./ml. are definitely resistant to amphotericin B. Since this is empirical and since clinical correlations between in vitro susceptibility and clinical response to treatment are not yet available, the only plea at present is for standardization of the method of performing susceptibility tests so that clinical correlations may eventually be made.

Hair Sprays Found Not Harmful

Tests by U. S. Food and Drug Administration pharmacologists have failed to demonstrate harmful effects from repeated inhalations of aerosol hair spray preparations. The FDA investigation followed a recent report in the *New England Journal of Medicine* linking pulmonary alveolar proteinosis in women with repeated exposure to inhalation of hair sprays for extended periods of time. FDA officials say that Federal laws, at present, do not require premarketing safety tests for cosmetics, although such tests are mandatory for all new drugs, pesticides, and food additives. New legislation to include cosmetics is expected to be introduced at this session of Congress.

SEX REVERSAL. A painstaking study of chromosomal sex in 3715 babies born in a Winnipeg hospital showed that all the 1804 apparent females were confirmed as having the right genetic sex; 5 of 1911 apparent males proved to have female nuclear sex (Lancet 1:217, 1959). One theory is that these "reversed" males were female at fertilization but that during fetal life some abnormality of development caused the appearance of testes; the cause might be an abnormal metabolism of maternal or placental hormones, which results in the production of androgens.

NEW ANTIHYPERTENSIVE. A new reserpine-like hypotensive agent, syrosingopine (Singoserp, Ciba), is reported to be as potent as existing Rauwolfia compounds and considerably less toxic. It is indicated especially for hypertensive patients requiring little or no sedation to reduce blood pressure. When combined with more powerful hypotensive agents, the new drug permits using them in lower than usual dosages.

PROTECTION AGAINST RADIATION. A crude yeast autolysate given prior to lethal irradiation provided a moderate degree of protection in mice against the effects of radiation (Science 128:656, 1958). According to preliminary results, ribonucleic acid, or a substance associated with it in the yeast autolysate, appears to be the most important factor.

VITAMIN-HORMONE REGIMEN FOR GERIATRIC PATIENTS. A total of 113 geriatric patients with organic diseases were treated with a preparation containing low estrogen-androgen concentration combined with iron, vitamins, minerals, amino acids, and pancreatic substance (Neobon, Roerig). Ninety-eight patients responded well to treatment, with increased appetite, more energy, elevated hemoglobin value, and improved feeling of well-being. Only 15 patients showed no improvement.

PASTEURIZATION OF HUMAN MILK. Pasteurization and freezing of human milk apparently has no effect on its nutritional value, according to a recent report (Pediatrics 22:935, 1958). The relation of nitrogen intake to nitrogen retention was similar for 10 infants fed fresh milk to that found in previous studies for infants fed pasteurized human milk. In 4 infants who initially received fresh human milk by bottle and were later fed pasteurized human

milk, nitrogen intakes and retentions were similar during both types of feeding.

DRUG EFFECTIVE IN PETIT MAL CASES. Distinct clinical improvement was observed in 15 of 16 children with petit mal after treatment from 3 to 31 months with the antimalarial quinacrine hydrochloride (Atabrine, Winthrop) (Scottish M. J. 3:441, 1958). Six children became asymptomatic and symptoms were less marked in the remaining 9. Definite improvement in severity and frequency of attacks was noted within a few days after therapy was started.

TOTAL SYNTHESIS OF ANTIBIOTIC ACHIEVED. The total synthesis of a tetracycline that has biological activity has been achieved at Lederle Laboratories Division, American Cyanamid Co. (J. Am. Chem. Soc., Feb. 20, 1959). In a series of 30 chemical reactions, the chemists produced a derivative of demethylchlortetracycline, an antibiotic previously available only by fermentation of living organisms. The significance of the synthesis is that it may pave the way for the construction of new antibiotics that cannot be derived from living organisms.

OVARIAN THERAPY. A long-acting sterile hormone preparation (Deluteval, Squibb), formulated to help restore normal ovarian function, combines hydroxyprogesterone caproate (Delalutin) and estradiol valerate (Delestrogen). Administered intramuscularly, it is indicated in habitual abortion or threatened abortion; for nonpregnant women the drug is indicated in menstrual disturbances.

PSYCHOSOMATIC FACTORS IN TB RELAPSE. Psychosomatic factors play a strong role in relapse to infectious sputum among tuberculosis patients, reported a research team from the University of Washington (Seattle) to the American Foundation for Clinical Research meeting in Carmel, Calif. In contrast to control patients (who remained negative or free from tubercle bacilli), relapsing patients' histories were marked by consistent lack of adjustment to life situations, and their reactions to problems encountered in the hospital often resulted in emotional upheaval.

CATARACT AND USE OF EYES. Persons with developing cataracts need not fear that intensive use of the eyes will speed the course of the disease, according to James F. O'Rourke, National Institutes of Health. Theoretically, he said, use of the afflicted eye may even slow down cataract development because most body tissue tends to resist deterioration when kept in use.

Antibiotics in the Therapy of Hodgkin's Disease and Related Malignant Processes

John R. Sampey, Ph.D.
FURMAN UNIVERSITY
GREENVILLE, S. C.

Antibiotics have been employed in the management of Hodgkin's disease and allied malignant processes.[61, 62] In many of these clinical trials the drugs have been combined with transfusions, radiation, and other chemotherapeutic agents. The present study is limited to antibiotic therapy alone or in connection with radiation.

Hodgkin's Disease. Antibiotics have been ranked as the third most frequently used chemotherapeutic agent in the control of Hodgkin's disease.[61] Of 43 patients on actinomycin C, Schulte[64] reported the best results in 17 who had had no previous therapy, but 22 of 26 previously treated showed some improvement, and radiation shortened the period of antibiotic therapy. In another study, Schulte[65] noted that 11 of 33 patients on radiation and actinomycin became symptom-free, while 4 of 26 on the antibiotic alone had relapses of 18, 8, 8, and 7 months, respectively; 18 others recovered, and 4 died.

Ravina and associates[54–58] have released five reports on antibiotic therapy of Hodgkin's disease. They reported good remissions in 26 patients on actinomycin C in 1954 and 60 per cent response in the initial phases of Hodgkin's disease in 1955; in 1956 they added 2 more good remissions with actinomycin C therapy.

Croizat[19, 20] conducted two investigations on actinomycin C therapy of Hodgkin's disease. In 22 cases of blood diseases (16, Hodgkin's disease) he recorded 8 good responses, but 6 patients suffered severe diarrhea, and he concluded that the results were inferior to those with radiation or nitrogen mustard therapy. In 1955 he recorded that 13 of 23 patients with Hodgkin's disease showed a decrease in fever and an increase in appetite, but no change in the blood picture.

Barnard and associates[1–6] conducted six studies on the therapy of blood malignant processes with antibiotics. They employed crude extracts of oxytetracycline, streptomycin, and other antibiotic drugs in a five-year investigation of Hodgkin's disease, leukemia, and lymphomas. In one study they reported that 9 of 21 patients with Hodgkin's disease showed a good palliative response.

Actinomycin C failed to influence the course of radiation therapy of 20 cases of Hodgkin's disease, according to Schwenkenbecher and Hillger,[66] and Gaitan Yanguas and Campbell[26] concluded that the use of this antibiotic was not justified in 20 other cases. Huguenin[30] noted slight, temporary effects in only 4 of 21 patients on actinomycin C, and one year later,[31] he added 3 more failures in children with Hodgkin's disease. Vogelgesang and Tobben[71] noted subjective improvement in 76 per cent of his patients on actinomycin C therapy.

In two studies, Martin obtained some response with actinomycin C, reporting 3 good and 4 fair remissions in 24 cases[42] and 4 satisfactory remissions in another

12 cases.[43] Kubasta et al[35] recorded 4 good and 7 fair responses in 15 patients on this same antibiotic, and Bertrand-Fontaine et al[8] described 1 notable and 2 fair responses in 15 patients. Sandor et al[63] gave few details in his report of good palliation in 15 patients given actinomycin C therapy, and Eckhardt et al[21] likewise gave little data on the type of response in 7 of their 13 patients under this therapy. Field[22] noted partial response in 4 of 11 patients on actinomycin C therapy, which lasted up to 4 months. Magnus and Zeitter[41] claimed subjective improvement almost always after the use of actinomycin C in 13 patients, and they observed longer remissions after roentgen-ray doses, lasting up to 18 months. Clatro Sagastume and Baron[16] gave few details of the response noted in 10 patients on actinomycin therapy. Bollag and Esselier[10] concluded that actinomycin C was inferior to other drugs and radiation therapy after obtaining only slight responses in 3 of 8 patients on actinomycin C. Tapie[68] noted some favorable reaction in 7 patients on the same drug.

Several investigators reported responses in smaller groups of patients. Korst and Meyer[37] claimed no remission and little improvement in 3 patients after using actinomycin D. Trounce et al[70] observed 1 marked and 2 slight regressions in 6 patients on actinomycin C, and Osten and Zademack[51] described 3 fair reactions in 6 patients with the same antibiotic. Olmer[50] listed 4 remissions in 5 patients with Hodgkin's disease, but some were not achieved until radiation or cortisone therapy was added. Cantero et al[14] had 3 of 5 patients respond to crude extracts of penicillin and *Aspergillus*, and Otto[52] tabulated 2 good responses in 3 patients on actinomycin therapy. Gernez-Rieux and Goudemand[27] reported good results in 3 of 4 cases and fair response in the fourth after actinomycin treatment; in a second report[28] they described brief response in 1 of 3 cases. Boon[11] achieved good hematological and clinical response in 1 patient on actinomycin C, and Brown[13] observed a patient whose blood picture remained normal for seven years on chloramphenicol management. Johne and Kroher[33] maintained 1 patient in good remission on combination actinomycin C plus penicillin and streptomycin therapy, and Funk and Krober[24] described a good clinical remission on actinomycin C. Brief palliative control of Hodgkin's disease with the same antibiotic has been recorded by Causse,[15] Lopez-Sendon and Rey,[40] Mokrzycki,[46] Nitsch and Thein,[49] and Zakl.[73] Goldman[29] detected no alteration in the clinical course of Hodgkin's disease in 4 patients on chlortetracycline therapy, and Rottino et al[60] found no beneficial effects in 7 patients after use of this same antibiotic.

Acute Leukemia. Food supplements obtained by fermentation with *Streptomyces* were given orally to patients with acute leukemia by Barnard;[3] he noted that the clinical picture was often improved even through the blood condition was not altered. In another study,[2] he described improvement in 18 of 29 patients on the same therapy, and in a third investigation,[4] he warned of the danger of congestive failure and diabetes in antibiotic therapy.

Huth[32] secured partial hematological remissions in 5 patients with myeloblastic leukemia after use of chlortetracycline. Brief responses in acute leukemia were reported by Field[22] and Lacroix et al[39] in 2 of 3 patients given actinomycin C. Plauchu et al[53] observed the control of infections in 3 leukemic patients on chlortetracycline, but no effect on the outcome of the disease. No beneficial results were ascribed

to this same drug in 1 case of acute leukemia[60] or in 2 patients on actinomycin C therapy. Tondi[69] reported the development of a lymphosarcoma in a patient with acute leukemia who was given radiation and penicillin therapy.

Chronic Leukemia. Begemann[7] recorded good clinical remission and reduction in both leukocytes and lymphocytes in 3 of 12 patients with chronic lymphocytic leukemia on actinomycin therapy. Bousser and Jallut[12] ascribed a fair response to streptomycin therapy in 1 patient with the same condition, but little or no improvement was recorded with actinomycin C treatment in 1 case by Eckhardt et al,[21] by Field[22] in 3 cases, by Kasdorf and Ferrari[35] in 2 cases, by Kubasta et al[38] in 5 cases, and by Otto[52] in 1 case of chronic lymphatic leukemia. Penicillin failed also in 1 case according to Friedman.[23]

Chronic myeloid leukemia responded little better to actinomycin C management, according to Field[22] and Lacroix et al[39] in 1 case each and Ravina[56–58] in 3 cases. Magnus and Zeitter[41] noted subjective improvement in 3 chronic cases on actinomycin C.

Lymphosarcoma. Actinomycin C induced remissions in 6 lymphosarcoma patients in a report by Croizat,[19] but he judged the results less satisfactory than those with radiation or nitrogen mustard. Kasdorf and Ferrari[35] claimed a moderate response to this antibiotic in 5 cases, and Eckhardt et al[21] judged the same in 1 case. Some palliation was observed by Barnard[4] in 1 patient on oxytetracycline, by Tan et al[67] in a patient on actinomycin D, and in 1 patient on penicillin and radiation therapy by Neuberger and Werkgartner.[48] No effects of actinomycin were recorded in 4 cases by Huguenin et al,[30] and none in 1 patient on chlortetracycline by Rottino et al.[60]

Reticulosarcoma. In two investigations on the action of actinomycin C in patients with reticulum cell sarcomas, Croizat[19, 20] reported that only 2 of 10 were helped in one group, and there was some response in 4 others. Cantero et al[14] called attention to a favorable reaction in 3 of 4 patients on crude extracts of penicillin, and Eckhardt et al[21] observed a remission in 1 of 2 patients with actinomycin C. Olmer[50] and Ravina and Pestel[56] noted some regression with actinomycins. Marked improvement was described by Trounce et al[70] in 1 patient on actinomycin C, but Kubasta et al[38] recorded no effect in 2 cases with this drug.

Mycosis Fungoides. Cortella[17] recorded a case of mycosis fungoides that was managed for years with actinomycin C and small dosages of radiation. Funk and Krober[24] noted some response to actinomycin in 1 case, but Witz[72] found complete failure with sulfonamides and penicillin therapy in 2 patients.

Myeloma, Multiple Myeloma, and Melanoma. Kubasta et al[38] reported that actinomycin C was without effect in 1 patient with myeloma. Coste et al[18] described 1 of 3 patients with multiple myeloma in whom the blood picture became normal, pain subsided, and general improvement was noted after chlortetracycline treatment. Field[22] observed some response in 1 patient with multiple myeloma on actinomycin C therapy. Moore et al[47] estimated 50 per cent regressions in 2 melanoma patients after trials with actinomycin D.

Miscellaneous Lymphomas. Moore et al[47] also recorded 50 per cent regressions in 3 patients with lymphoblastoma after actinomycin D treatment, and Kabisch[34]

TABLE I

Summary of Results with Antibiotic Therapy for Hodgkin's Disease and Related Malignant Processes

Malignant process	Cases	Good response	Fair response	Bibliographic reference
Hodgkin's disease	447	83	95	38
Acute leukemia	44	—	25	10
Chronic leukemia	34	3	4	12
Lymphosarcoma	20	—	9	8
Reticulosarcoma	23	1	6	8
Mycosis fungoides	4	1	1	3
Myeloma, multiple myeloma, melanoma	7	1	3	4
Miscellaneous lymphomas	30	4	13	9

observed good palliation with radiation and actinomycin C in 3 patients with Brill-Symmers disease. Ravina and Pestel[56] noted a good response in a patient with this same neoplasm under the same therapy, but Riegel and Kruckemeyer[59] classed the response as only fair in 2 other cases. Bierman et al[9] induced marked improvement in identical twins with Letterer-Siwe disease after the use of four antibiotics, chlortetracycline, chloramphenicol, streptomycin, and penicillin: there was regression of anemia and roentgenographic evidence of healing and disappearance of osteolytic lesions after 15 and 23 months, respectively. Keller[36] noted that lymphoid leukemia of the skin responded clinically to penicillin, while Miescher and Storck[45] classed as good another response with this same antibiotic. One of 10 patients with Wilms's tumor demonstrated regression in lung metastases and stomach tumor mass, and 3 of 6 neuroblastomas improved subjectively and objectively after actinomycin D therapy.[67] Lacroix et al[39] reported no benefit from actinomycin C in a case of lymphoblastoma.

SUMMARY

Table I summarizes the antibiotic therapy of more than 600 patients with Hodgkin's disease and related malignant processes. The results were better than they appear from the data, for a number of reports listed the number of patients treated without giving any data on the number responding, even when the results were classed as good. This is especially true of Hodgkin's disease, where one fourth of the 447 cases have no tabulations on the effect of antibiotic treatment, but a total of 83 good and 95 fair responses indicates that the therapy is useful in the control of the disease. The number of trials in related diseases is too limited for the results to have statistical value, but further testing of miscellaneous lymphomas should be especially promising as new antibiotics become available.

ACKNOWLEDGMENTS

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Library of Medicine and the libraries of Furman University and Greenville General Hospital.

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SYMPOSIUM ON MEDICINE AND WRITING

The Symposium on Medicine and Writing that appeared in the November 1956 issue of International Record of Medicine has been published recently as a Monograph. The articles included in this Monograph are: "The Editing of a Modern Medical Textbook" by Russell L. Cecil; "Plain Talk and Clear Writing" by Morris Fishbein; "The Principles of Bibliographic Citation" by John F. Fulton; "The Art of Communication" by Joseph Garland; "On Writing a History of Medicine" by Douglas Guthrie; and "Minerva and Aesculapius: The Physician as Writer" by Félix Martí-Ibáñez.

This 72-page Monograph is sold for $3.00. As the fourth in the series of MD International Symposia, this book is the companion piece of *Medical Writing*, which was published in May 1956.

To obtain this monograph, write to MD Publications, Inc., 30 East 60th Street, New York 22, N. Y.

The Phenomenon of Resistant Colonies Within the Inhibition Zone

Rafael Gómez Lus, M.D.

ASSOCIATE PROFESSOR, DEPARTMENT OF MICROBIOLOGY, SCHOOL OF MEDICINE
SARAGOSSA, SPAIN

We should like to report on a very interesting phenomenon we have noted while studying antibiotic sensitivity, and which we think is of great importance with regard to the resistant strains that appear during antibiotic treatment.

In a strain of *Neisseria meningitidis*, we observed an inhibition zone for penicillin, which would indicate that the organism was sensitive to penicillin. However, within the inhibition zone, we observed several resistant colonies (fig. 1). We repeated the sensitivity studies with these colonies several times and we found that the organisms maintained their resistance across the subcultures. However, on repeating the experiments with subcultures from outside the inhibition zone for penicillin, we found the same phenomenon just described.

Later, we observed a similar phenomenon on studying several strains of *Micrococcus pyogenes* var. *aureus*, coagulase-positive and penicillin-resistant. We found some colonies of these organisms inside the inhibition zone for the broad-spectrum antibiotics.

The strain of *N. meningitidis* was isolated from a patient with meningitis. The organism belonged to serogroup A; antibiotic sensitivities were as follows: sensitive to chloramphenicol, chlortetracycline, oxytetracycline, tetracycline, erythromycin, and carbomycin; resistant to streptomycin and sulfadiazine; resistant colonies within the inhibition zone for penicillin. A diagnosis of tuberculous meningitis was made. The patient was placed on streptomycin and his condition improved. Approximately two months after treatment, he began to show meningeal signs again and the same symptoms as were seen at the beginning of the disease. A strain was isolated, and the patient was given penicillin for two weeks. Because there was no improvement, a spinal tap was taken, and the same strain was again isolated. With the organism isolated the first time, we saw resistant colonies within the inhibition zone, but with the second isolation, the *N. meningitidis* was completely resistant to penicillin, probably because the antibiotic killed the susceptible organisms. On studying these strains of *N. meningitidis*, we noted that the biochemical and serological properties of both organisms were the same. Thus we were able to observe in vivo that the phenomenon of resistant colonies within the inhibition zone is something of an intermediate step between the primarily sensitive organisms and the finally resistant mutants.

In the case of the staphylococci, we studied four strains exhibiting two types of phenomena:

1. Resistant colonies within the inhibition zone for the following antibiotics: chloramphenicol (C), chlortetracycline (A), oxytetracycline (T), and tetracycline (Z); sensitive to: erythromycin (E), oleandomycin (O), carbomycin (Ca), and novo-

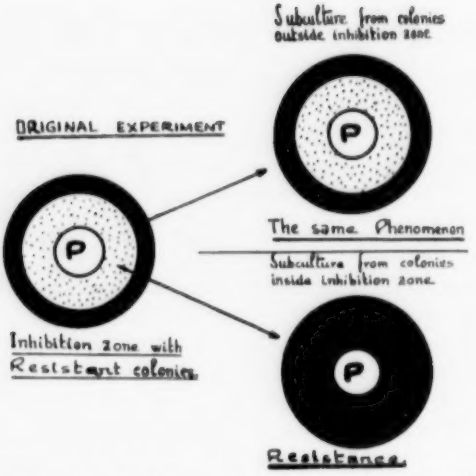

FIG. 1. Resistant colonies within the inhibition zone for penicillin with a strain of *N. meningitidis*.

biocin (N); and resistant to: penicillin (P), streptomycin (S), neomycin (Ne), and bacitracin (B) (figs. 2 and 3), for two strains of *M. pyogenes* var. *aureus*, coagulase-positive, one isolated from a patient with bronchitis and the other from a patient

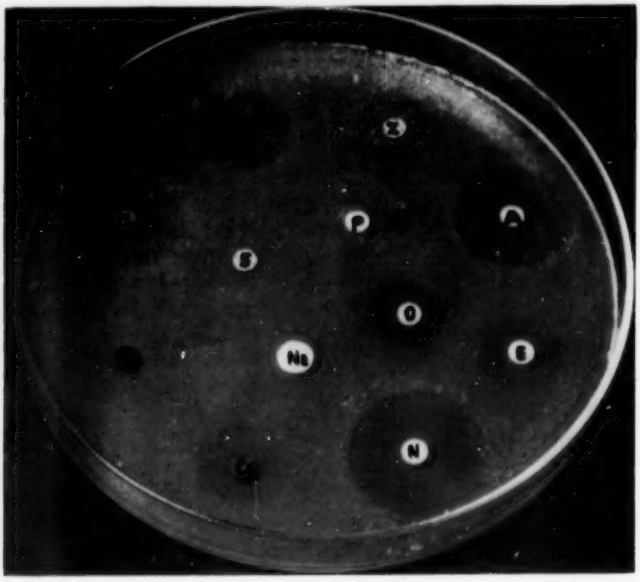

FIG. 2. Sensitivities to antibiotics of a strain of *M. pyogenes* var. *aureus*. See text for key.

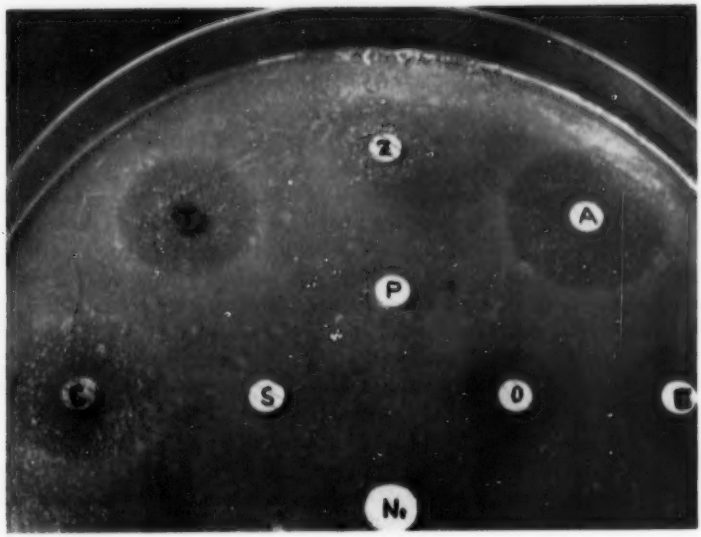

FIG. 3. Sensitivities to antibiotics of a strain of *M. pyogenes* var. *aureus*. See text for key.

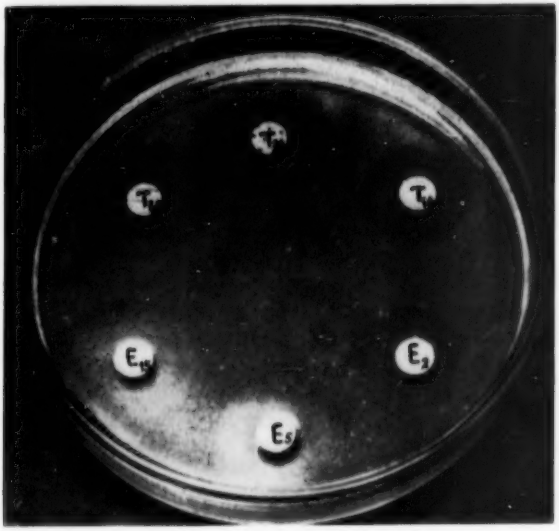

FIG. 4. Resistant colonies within the inhibition zone with low, intermediate, and high concentrations of antibiotics. See text for key.

with anthrax. The resistant colonies within the inhibition zones were similar with low, intermediate, and high antibiotic concentrations (fig. 4). We made several subcultures with the organisms found inside the inhibition zones of the four antibiotics mentioned. All the organisms of these subcultures were resistant to the four antibiotics. The mutants conserved all their biochemical properties. Thus, we see that there is cross-resistance between the tetracyclines and chloramphenicol. The only antibiotic treatment the patient with bronchitis received was penicillin and streptomycin, for two weeks before the *M. pyogenes* was isolated. That is why we think that the microorganism had resistant colonies within the inhibition zone when the patient contracted the infection. On the other hand, the patient with anthrax received chloramphenicol, chlortetracycline, and oxytetracycline several times before the isolation of the strain. Probably the resistant colonies within the inhibition zone were acquired during treatment.

2. Resistant colonies within the inhibition zone for the three following antibiotics: chlortetracycline, oxytetracycline, and tetracycline; sensitive to: erythromycin, oleandomycin, carbomycin, and novobiocin; and resistant to: penicillin, streptomycin, chloramphenicol, neomycin, and bacitracin, for two strains, one isolated from a patient with otitis and the other from a patient dying from sepsis. In this group there was no cross-resistance between the tetracyclines and chloramphenicol, as contrasted with the previous group. The antibiotics used for the patient with otitis before the isolation of the organism were penicillin, streptomycin, and chloramphenicol. This patient was treated with chlortetracycline for three weeks. He improved slightly. At that time we took a new culture, and we were able to isolate the same strain of *Staphylococcus*. This organism had the same sensitivity to the antibiotics, except that it was resistant to chlortetracycline, oxytetracycline, and tetracycline, and there were no resistant colonies within the inhibition zone. This is similar to findings with the *N. meningitidis*, but here the antibiotics were tetracyclines instead of penicillin. We do not know what treatment was used for the patient who died from sepsis.

In regard to our experiments with rabbits, we will describe bacteriophage typing, mutation rate, morphological changes, and other details in our final report.

We would explain the phenomenon of resistant colonies within the inhibition zone in these terms: Part of the bacterial population is sensitive to the antibiotic, producing the inhibition zone, and the other is resistant, explaining the resistant colonies within the inhibition zone. We have had the opportunity of observing this phenomenon both in vitro and in vivo, and we think it is very interesting from both the theoretical and practical points of view. We will continue our studies on this subject, but for the moment we feel that the phenomenon is sort of an intermediate step between the primarily sensitive organism and the finally resistant mutants, in penicillin-type resistance.

The Epic of Medicine (I)

PRELUDE OF MIST*
(Prehistoric and Magic Medicine)

Félix Martí-Ibáñez, M.D.
PROFESSOR AND DIRECTOR OF THE DEPARTMENT OF THE HISTORY OF MEDICINE,
NEW YORK MEDICAL COLLEGE, FLOWER AND FIFTH AVENUE HOSPITALS;
EDITOR-IN-CHIEF OF MD MEDICAL NEWSMAGAZINE
NEW YORK, N. Y.

And from the remote mists of Time there emerged some solitary humanoid creatures who started a hard wandering life over the face of the earth. Between these the first prehistoric men—polished links in a long biological chain—and the original amorphous amoeba there already existed a distance of millions of years.

There was little difference between the preceding anthropoids—our cousins, the apes—and the first prehistoric men, except that when the latter descended from the trees and learned to walk on two feet, they lost their powerful strength of jaw and abdominal muscles, and instead developed a larger cranium to accommodate a heavier cerebral mass. Of these creatures there remains only the testimony of fossils, weapons, tools, and the paintings they did by torchlight on the dripping walls of their caves.

Impelled by hunger, cold, and fear, these creatures roamed the vast natural tapestry of desolate land and steaming jungle, under the silent threat of the myriad eyes that flashed in the immense black velvet of the heavens.

Even before man appeared on the earth disease already existed among beasts. Fossils, bones, and teeth tell the tragic tale of prehistoric man succumbing to disease. A sickly man indeed he must have been, his body and mind wasted by sleeping on the cold, mud-tainted ground, which he shared with snake and toad, by lack of food, by traumas, fears, and stresses. A versatile hunter, he used animal teeth and horns as weapons, and he communicated with his fellow creatures through grunts, gestures, and blows. Two revolutionary discoveries—the flint axe, a stone fingernail that spared his own torn and bleeding nails, and the leather handle subsequently attanched to the axe—changed his life, which was further facilitated by the scarlet mystery of fire.

The first physician was man himself; the first medicine, his own instinctive attempts at self-healing, licking, sucking, and blowing on his lesions. When these individual reactions became stereotyped, the ritual became as important as the treatment. Accidental or battle wounds, cutting up animals, and cannibalism gave man an idea of the visceral content of the human body, as revealed by paleolithic paintings in which the heart is shown as the best spot to strike a mortal blow. And when man began to eat animals' organs, the principle of opotherapic similitude was born.

Former weapons began to be used to make incisions and trepanations. Licking and sucking were replaced by bloodletting, scarification, amputation, and surgery

* This editorial originally appeared in *MD* Medical Newsmagazine, May, 1959. It is the first of a series of twelve devoted to presenting a philosophical outline of the history of Medicine.

with stone tools. Covering fractures with mud, in imitation of monkeys, provided the first natural cast when the mud dried. And the discovery of fire brought with it burns, but also cautery. A powerful sociological agent, fire beckoned human creatures to gather together in its warm, golden chambers.

Disease developed according to mechanisms identical to those that prevail today: alterations in growth and metabolism, tumors, traumas, and infections. Fossils and carved stones imprisoned the message conveyed by this primigenial humanity, which roamed the earth before the beginning of history.

Millennia passed, and out of the prehistoric mists there emerged neolithic man, who, upon learning to grind and shape stone and turn it into weapons and tools—the missile and the hammer—ushered in somewhere around 12,000 B.C. the history of civilization. These primitive men we know through carved stones, myths and legends, and the magic thought of the primitive tribes of today, people isolated in an isle of Time.

Neolithic man—Caucasians, Mongoloids, and Negroids—lived in Europe and Asia, in a world that was turning temperate and humid and where, there being no notion of distances, incredibly long trips were undertaken on foot. Respect for the laws of Nature was born as the only way to conquer it; biologically correct social habits were developed; and community life began. In the endless nights, primitive man (isolated man is perhaps a better term) created astrology and astronomy and came to know the heavens before he conquered the earth. He also devised a mathematical system based on counting his fingers and toes; he learned to use the wheel; lining a basket with mud, he discovered ceramics; he polished stone, horns, and bones, cultivated plants, domesticated animals, and invented textiles.

Diseases—respiratory, osteoarthritic, gastrointestinal, genitourinary, traumatic, arteriosclerotic, infectious, and mental—were treated if minor with domestic remedies (diet, herbs, plasters, massage), often in imitation of wild animals; if severe, like smallpox, serious fractures, psychoses, the patient was killed to relieve the community of his burden, or the healer was summoned.

Besides empirical healers, who employed physiotherapeutic methods, there was the medicine man or shaman, usually a psychopath or schizophrenic, who practiced exorcism, made prophecies, and combined the functions of physician, magician, priest, statesman, and troubadour. The shaman's technique was based on magic. Magic was the precursor of science, man's first attempt to understand Nature. Preventive magic considered disease as a *plus* (entry in the body of a foreign object or spirit) or a *minus* (subtraction of the soul by magic).

The main techniques of the shaman were homeopathic magic, based on similitudes; contagious magic, based on destruction of the enemy; and direct magic, which required special rituals to prevent disease. Defensive magic used *fetishes* (objects endowed with magical powers); *amulets* (protective objects against black magic); and *talismans* (good luck objects). The shaman based his diagnosis on the concept that there was only one disease, which he identified with the cause; the "clinical history" consisted in an interrogation on the existence of fetishes, evil dreams, or broken taboos; prognosis depended on auguries and oracles; treatment was based on the aforementioned concept of intrusion of a foreign object or spirit, or subtraction

of the soul. Once the direct cause was determined (magic, witchcraft, death dreams, or moral delinquency), intrusion by a foreign object was treated by magic, sucking, extraction rituals, massage, baths, or vegetable drugs; and possession by a spirit, by exorcism, bloodletting, and spells.

The herbalist and prophet, therefore, coexisted with the shaman, who emerged from the millenary mists as the first medicine man, priest, and artist, in whom were joined Medicine, Religion, and Art, knowledge, belief, and creation. His magic was an art of arts, which attempted to govern the demons. It was a pseudoscience, based not on rational observation, as science is, but on the shaman's own experience of emotional states. It sought to treat human-produced and supernatural causes through mechanistic and psychological magic rituals, based on analogies and not on experiment; and "natural" causes through empirical resources, such as setting fractures, giving medicinal herbs, isolating the "possessed" (infectious or mental), practicing cranial decompression to expel the demons in an epileptic, and variolation. To combat disease, the shaman used sucking, bloodletting, and cupping, accompanying his treatment with dramatic gestures and much drum-beating and rattle-shaking, until the "culprit" incarnating the disease, usually a pebble or tiny insect, was suddenly produced and the patient was declared cured. Other times the shaman used professional "soul catchers" to retrieve the wandering soul of the patient. And in all cases he practiced verbal psychoanalytical exorcism.

Magic medicine, which still prevails in present-day primitive communities, avoided harming the patient and accepted the existence of a psychic component in all diseases. Therapy was of a cathartic nature (bloodletting, purgatives, diuretics). Thus, magic medicine was based on the *who* (the personality of the shaman), the *where* (the sacred place for his rituals), and the *when* (the magic hour); just as scientific medicine today is based on the *what* (what is done), the *how* (the technique used), and the *why* (etiological motive of the therapy).

Seeing and *believing*—empirical experience and mystic faith, natural medicine and magic—these were the first two attitudes adopted by man when confronted with the mystery of disease. These two great channels—*empirical* and *magic*—through which flowed primitive medical thought, would later be widened by the current of *thinking* and *knowing:* the *rational* knowledge of disease and of its treatment.

A man of culture, power, and prestige, the shaman was the first statesman and leader and the most brilliant man in his community. With his attempts at healing he gave man, who ignorant and helpless was a victim of his physical frailties, the first chance to face and solve the riddle posed by the sphinx of disease in the prelude of mist to the Epic of Medicine.

BOOK REVIEWS

No More War. LINUS PAULING. New York, Dodd, Mead & Co., 1958. Pp. 254. Price $3.50.

The greatness of a book is closely linked to its purpose. Here is a book of greatness, whose sole purpose is peace among men and cooperation among nations for the progress and welfare of mankind. It has been written by a world-famous scientist whose Aristotelian mind encompasses not only the vast dominions of chemistry and physics, but also those of geology, biology, and medicine. The thesis of *No More War* is formulated in a clear, ringing voice; its tools are a terse, lucid prose and an immense chest full of terrifying facts. War as a solution to world problems, says the author, must be abandoned immediately. Instead it must be replaced by international agreements. On the way to that ideal are interposed gigantic obstacles raised by scientific forces of evil. To make the reader aware of the cataclysmic results of war waged with the new hydrogen weapons, Dr. Pauling presents with diaphanous clarity the nature of nuclear weapons and the processes of fusion and fission, the dangers of radioactivity and fallout, and the effect of radiation on heredity and health. In that apocalyptic picture he includes a word etching of the results of atomic war today. Figures speak with a marrow-chilling eloquence: at the end of sixty days of atomic war, about three quarters of the population would be dead in this country, and in the world between 500 million and 750 million persons would die. A world of confusion and chaos, death and devastation emerges out of the atomic smokes in this book, which by comparison turns Dante's Inferno into a delight. But the author has faith in the forces that can help to prevent war, and especially in one that to us physicians is the very basis of our credo: *morality*, and with it goodness and humanitarianism, the power of the human spirit, greater than that of any hydrogen weapon. He proposes the creation of a World Peace Research Organization based on these forces, a universal brotherhood of men of science working together for peaceful and progressive purposes, a world university of morality and dedication to the great causes of mankind. His forceful plea is reinforced in the appendixes to the book, which include warning words from Albert Einstein and Albert Schweitzer also for the cause of peace. It is highly symbolic of this important book that its author, who won the Nobel Prize for Chemistry for his work in determining the nature of chemical bond, is now working with equal dedication to create a bond of love and cooperation among men in our time.

—*Félix Martí-Ibáñez, M.D.*

A Search for Man's Sanity: The Selected Letters of Trigant Burrow with Biographical Notes. Foreword by SIR HERBERT READ. New York, Oxford University Press, 1958. Pp. 615. Price $8.75.

The publication of the selected letters of Trigant Burrow will be welcomed by those who are familiar with his work; they will also serve their purpose as an authentic introduction to Burrow's "phylobiology." The reader is able to trace the origins, the elaboration, and the final version of Burrow's thesis, considered by Sir Herbert

Read, who wrote the foreword, as "surely something very simple, very comprehensible, and overwhelmingly important. It points to the anciently recognized truth that man is not a detached particle of life, pursuing a separate orbit, but that we are part of one another. From that fact it follows that the analysis of the individual can never be completed without a consideration of the group of which he is an organic part. His very resistances to analysis are *social* resistances, and it is these social resistances, buried deep in the unconscious, that must be exposed . . ." (p. IX). It was this social and all-pervading nature of man's resistances and neurosis that impressed Burrow in his early days and prompted his search for a new frame of reference, once the physician was recognized by him as included in the "social neurosis" and subsequently deprived of his claim to be the trustee and representative of the norm.

The new audience addressed by Burrow embraced mankind as a whole, the physician himself emerging as a patient in dire need of overcoming the social resistances. "It is the people who need help for themselves and who accept the humiliation of their need and have the full recognition of it to whom we have anything of interest and renewal to offer . . ." (p. 118). Almost 25 years later, Burrow framed his mature and final thought in the following words: ". . . coincident with man's acquisition of the symbolic function (a function that has, of course, been of incalculable benefit to man in the course of his evolution), he has acquired a false sense of the self and of the behavioral norm which regulates the interactions of the individual with others of his kind" (p. 537). The interindividual conflict in man, however, should not be identified with the spontaneous biological antagonisms existing at lower evolutionary levels (*loc. cit.*). This qualification seems of no small importance, since it protects the rapid reader from simply identifying Burrow's thesis with the well-known eighteenth century tendencies to let man's history begin with that of the "noble savage" and to call for a simple return to his genuinely natural condition.

In man, Burrow says, "the parental generation has put the younger up to 'rights' or prerogatives for which there is no biological foundation and which are answerable throughout human society for the ideological conflicts existing within and among us." He tried "to bring out evidence of the induction in man of an image of the self which is quite fantastic and which, in investing the child with an artificial sense of its preeminence . . ., automatically sets the stage for competition and conflict throughout the species" (p. 538). Here are the roots of Burrow's *social* concept of neurosis: ". . . the neurotic personality (and that is everybody) is unconsciously dependent upon mental images which have no substantiation but which have been artificially induced in him through the mental images of the people in closest contact with him" (p. 81). Evidently, the conflict arises within man himself, once he has gained his full stature of a human being. Nevertheless, it is not man's greatest endowment as such (his reflexive and symbolic thought), but only its misuse that led to the actual disrupture of interindividual relations; this misuse has its roots in man's affectivity or in a "misappropriation of feeling," due to which partial (cerebral) activities replaced the identity of the organism as a whole. Burrow thus was led to capture the internal physiological changes accompanying external behavior or, in his own terms, to study the biology of the human conflict.

The reader learns from the preface by the editors and the letters that instrumental studies were undertaken in the Lifwynn Foundation of respiration, brain-wave patterns, and eye movements and their relationship to behavior phenomena. In his group analytical and group therapeutical sessions, Burrow tried to recover on a physiological and psychological basis, "the total organism's internal feeling-behavior" (quoted from Read's discussion of Burrow's *Social Basis of Consciousness*, p. 173).

More than once Burrow tries in his letters to differentiate his own thesis from the views of the psychoanalytical school to which he originally belonged. These efforts can be traced, above all, in his letters addressed to Freud. In these as well as in all other letters one witnesses, often in pathetic terms, Burrow's search for truth and for man's sanity, his human figure standing out as that of a most sincere, kind, devoted, generous, and unresentful man, physician, colleague, friend, husband, and father. A significant chapter of the history of modern man is embodied in Burrow's life, work, and letters.—*Walther Riese, M.D.*

Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. HOWARD W. JONES, JR., M.D., AND WILLIAM WALLACE SCOTT, M.D., PH.D. Baltimore, The Williams & Wilkins Company, 1958. Pp. 456. Price $16.00.

This excellent book is a comprehensive review of our present knowledge of human hermaphroditism and related anomalies. Progress in the understanding and treatment of anomalies of sexual development has been especially rapid in recent years and therefore this thorough and authoritative book should be welcome to every physician.

The discussions of each type of anomaly are exceptionally complete from clinical features to diagnosis, treatment, and surgical correction when indiciated. Each chapter is documented with numerous case reports; excellent illustrations, particularly of surgical techniques, are included.

There are sections on the background of intersexuality, intersexuality with gonadal and chromosomal discrepancy, male intersexuality, female intersexuality, surgical treatment of hermaphroditism, genital anomalies simulating hermaphroditism, gonadal tumors with sex reversal, other adrenal disorders affecting sex.

New Research Techniques of Neuroanatomy. EDITED BY WILLIAM F. WINDLE, PH.D., SC.D. Springfield, Ill., Charles C Thomas, 1957. Pp. 98. Price $4.75.

This small book, the proceedings of a symposium sponsored by the National Multiple Sclerosis Society, contains reports of important research that is being done today in neuroanatomy.

Dr. Sanford L. Palay discusses electron microscopy and its use in research in the structure of the brain. Drs. Walle J. H. Nauta and Grant L. Rasmussen describe new strains for degenerating axons and a reliable technique for demonstrating synaptic endings, thus extending the value of silver staining methods to terminal processes of neurons and to nerve fibers.

Tissue culture studies of neural tissue are fully discussed by Dr. Margaret R.

Murray. Dr. Louis Sokoloff describes work done with his collaborators in the study of radioautography as applied to the central nervous system. Histochemical localization of acetylcholinesterase in nervous tissue is considered by Dr. George B. Koelle, while Dr. R. Wayne Albers reviews his enzyme work with the Linderstrøm-Land and Lowry techniques.

Although relatively brief, this symposium is valuable within its scope and presents a concise review of some of the new research techniques in neuroanatomy.

Home Care for the Emotionally Ill. HERMAN S. SCHWARTZ. London, Staples Press, 1957. Pp. 232. Price $5.00.

Written not for the professional nurse but for those who undertake to care for a mentally ill relative in the home, this book may at first glance appear to be merely a collection of platitudes. A careful reading, however, reveals its genuine value as a systematic presentation of many vital factors—from the all-important achievement of harmonious relations with the patient to specific therapeutic measures.

The author repeatedly emphasizes the importance of the attitude of the relative acting as "nurse" toward the patient, her encouragement and comfort, and her understanding of his reactions. It is pointed out that the relative must strike a balance between a too sympathetic approach—which would impair rather than speed the patient's progress—and the other extreme of complete detachment.

Included are chapters on making the patient comfortable, relaxation, the patient's appetite, work and play, psychological and spiritual aids, the alcoholic, the chronic patient, the aged.

Doctor Squibb: The Life and Times of a Rugged Idealist. LAWRENCE G. BLOCHMAN. New York, Simon and Schuster, 1958. Pp. 372. Price $5.00.

Texas Surgeon: An Autobiography. DONALD T. ATKINSON, M.D., New York, Ives Washburn, Inc., 1958. Pp. 180. Price $3.50.

These two books provide an interesting contrast—on the one hand, the biography of Dr. Squibb is a long, stuffy narrative, often dull and besieged by irrelevancies—all of which tends to diminish the luster of the really good and interesting passages—and on the other hand, Dr. Atkinson's story is simply told, understated, warm, and as interesting as a long chat with the author would certainly be.

About two thirds of this biography of Dr. Squibb consists of quotations from the voluminous journals he kept throughout his adult life, while one third is running commentary by the biographer. The main faults of the book arise from this arrangement, for Dr. Squibb's journal entries were day-by-day accounts of all the minutiae of his life recorded in such detail that the most stringent editing would be necessary to separate the interesting data from the many lists of nonvital statistics and other irrelevancies. This the editor has failed to do, and to make matters worse, instead of underplaying Dr. Squibb's mellifluent style of writing, the biographer adopts the same sticky tone.

The life of Edward Robinson Squibb was a fascinating adventure in both its pro-

fessional and private aspects. High-principled and idealistic, he fought throughout his life for purity and uniformity in drug standards and he refused to employ high-pressure promotional means to attract clients for the pharmaceutical house he founded. With his family, he was kind but stern, and he was to know much concern over his wife's health and his children's irresponsibility.

With such an interesting subject and a dozen thick ledgers of his journal to work with, the editor might have prepared a fascinating biography. If this book were 100 pages shorter, it might make quite a bit livelier reading.

The autobiography of Dr. Atkinson is a warm, straightforward, readable story. He tells of the long struggle to gain his medical education and experience, which led to final achievement of success and renown in his specialty of ophthalmology. He looks back on his full and adventurous life with understanding and humor, and his story is filled with a vitality and sincerity that make for very interesting reading.

Physical Methods in Physiology. W. T. CATTON, M.SC. New York, Philosophical Library, 1957. Pp. 375. Price $10.00.

This is a clear, concise manual of physical techniques used in physiology. The methods are described against a background of fundamental physiology, and such techniques as are frequently described in other books (e.g., electrocardiography, electroencephalography, special sense physiology) are not included here.

Among the valuable features of this book are excellent diagrams and charts and frequent cross-references within the text. Included are physical methods pertaining to the blood, the circulation, respiration, muscle, peripheral nerve, body heat exchanges, electronics in physiology.

The Chemistry of Blood Coagulation. PAUL MORAWITZ. Translated by ROBERT C. HARTMANN, M.D., AND PAUL F. GUENTHER, M.A., PH.D. Springfield, Ill., Charles C Thomas, 1958. Pp. 194. Price $4.50.

This book is an historical review of the blood coagulation problem and the advances made in this field since earliest medical history. As such, it has primarily historical rather than clinical application for the physician today.

Chapters are included on theories of blood coagulation before 1861, developments in the study of coagulation before 1890, the role of calcium salts in coagulation, thrombin and the clot-promoting substances in tissues, fibrinogen and fibrin, anticoagulants, clot-promoting substances, changes in the morphological elements of blood during coagulation.

A stilted translation from the German detracts from the book's interest. An excellent glossary is appended to the text.

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About the Author: Dr. Jacques M. May is head of the Medical Geography Department of the American Geographical Society in New York, where he has been engaged since 1948 in compiling the *Atlas of Diseases*, which comprises in the form of maps as comprehensive a presentation of the distribution of certain human diseases as available data will permit. Dr. May is a member of the staff of the Medical School of New York University in the field of preventive medicine and a visiting lecturer at the School of Tropical Medicine of Harvard University and at the School of Public Health of Columbia University.

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